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FACULTY OF PSYCHOLOGY AND
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Brain & Cognition

Of dots and digits.

Advanced neuroimaging techniques applied to the numerical brain.

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Cover created by Tine Van Passel. To whom I express my greatest gratitude.

Voor Jan.

Abstract

The objective of this dissertation is to progress our current knowledge of the neural correlates of number processing and impaired numeracy by applying advanced neuroimaging techniques. The application of these advanced techniques allowed us to directly address following pending debates in numerical cognition.

The first debate, is whether the different formats of a quantity (e.g., "2", ●●) have a unitary neural code. A first neuroimaging study investigated the possible overlap of Arabic digits and dots on multiple spatial scales with multivoxel pattern analyses and found no evidence for overlapping representations of Arabic digits and dots in the human cortex. A second neuroimaging study showed that the neural relationship between Arabic digits and dots was defined by the amount of objects that are presented, rather than by quantity.

Another debate, consists of the etiology of dyscalculia. One the one hand, it has been suggested that the neural number representations are impaired in dyscalculia. A third neuroimaging study showed evidence for impaired non-symbolic representations in dyscalculia. On the other hand, some studies also found impaired connectivity in dyscalculia. A fourth neuroimaging study applied structural and functional connectivity analysis and found evidence for altered connectivity in different neural circuits.

The third debate is on how number processing and arithmetic skills are correlated. Although most studies find a correlation of symbolic number processing and math achievement, the results for non-symbolic number processing are less consistent. We investigated this debate by applying multivoxel pattern analyses and found that the *level of overlap* of the neural representations of symbolic and non-symbolic numbers is negatively correlated with arithmetic skills.

To conclude, this dissertation comprises six studies demonstrating the strength of applying advanced neuroimaging techniques in numerical cognition. These new insights might eventually influence how we teach children the meaning of numbers, how learning strategies for mathematics develop, and how we can improve interventions for low numeracy.

Samenvatting

Het doel van deze thesis is het bevorderen van de kennis over de neurale correlaten van numerieke cognitie en zwakkere rekenvaardigheid door het toepassen van geavanceerde neuroimaging technieken. De toepassing van deze technieken liet toe om antwoord te bieden op volgende discussies in numerieke cognitie.
De eerste discussie, betreft of de verschillende formats van een kwantiteit (bv., "2", ●●) dezelfde neurale representaties hebben. Een eerste neuroimaging studie vond geen evidentie voor de overlap tussen neurale representaties van Arabische cijfers en dot patronen op verschillende spatiale schalen met behulp van multivoxel patroon analyses. Een tweede neuroimaging studie toonde aan dat de relatie tussen Arabische cijfers en dots eerder gekarakteriseerd wordt door de hoeveelheid objecten die gepresenteerd zijn, dan door hun numerieke waarde.
Een tweede discussie betreft de etiologie van dyscalculie. Enerzijds, is er gesuggereerd dat de neurale representaties van nummers gebrekkig zijn in dyscalculie. Een derde neuroimaging studie toonde aan dat er inderdaad gebrekkige non-symbolische representaties zijn bij mensen met dyscalculie. Anderzijds, is er ook evidentie gevonden voor connectiviteitsgebreken in dyscalculie. Een vierde neuroimaging studie onderzocht de functionele en structurele connectiviteit in dyscalculie en vond evidentie voor afwijkende connectiviteit in dyscalculie.
Een derde discussie stelt in vraag hoe numerieke cognitie en rekenvaardigheden samenhangen. Vele voorgaande studies vonden een correlatie tussen symbolische numerieke cognitie en rekenvaardigheden, maar de resultaten voor niet-symbolische numerieke cognitie is minder consistent. Door het toepassen van multivoxel patroon analyse, onderzochten we dit debat en vonden dat de *mate van overlap* tussen cijfers en dots negatief samenhangt met rekenvaardigheden.
In totaal bevat deze doctoraatsverhandeling zes studies die de meerwaarde aantonen van geavanceerde neuroimaging technieken voor numerieke cognitie. Deze nieuwe inzichten kunnen beïnvloeden hoe we kinderen de betekenis van cijfers aanleren, hoe leerstrategieën voor wiskunde verder ontwikkeld worden, en hoe we interventies voor zwakke rekenvaardigheden kunnen verbeteren.

Dankwoord

Ook al draagt deze thesis mijn naam, toch is het belangrijk om te vermelden dat er een heel team achter mij stond gedurende de jaren waarin ik aan deze thesis heb gewerkt. Deze mensen verdienen een welgemeende “dank je wel” voor al hun steun, hulp en vertrouwen in mij, want deze thesis was nooit tot stand gekomen zonder hen.

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people in the world who will have read my dissertation from the beginning to the end. Thank you for being here today to discuss my work, I look forward to your interesting questions.
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over connectiviteit; hoofdstuk 7 in deze thesis zou letterlijk niet zonder jou tot stand zijn gekomen. Heel erg dikke merci!

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andere verwezelijkingen zouden niet gelukt zijn zonder jou aan mijn zijde. Voor al deze dingen en voor alle liefde van de voorbije 13 jaar, en voor alle komende jaren, dank je wel. Om Billie Holiday te parafraseren, ik weet niet waar de weg ons naartoe zal leiden, alleen een zot zou dat kunnen, maar ik weet wel zeker dat het prachtige reis zal worden samen...

When somebody loves you
It's no good unless he loves you - all the way
Happy to be near you
When you need someone to cheer you - all the way

Billie Holiday - All the way

Jessica
Leuven, mei, 2017

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Abbreviations

AD	Axial Diffusivity
AF	Arcuate Fasciculus
AF_{FP}	Fronto-parietal Arcuate Fasciculus
AF_{FT}	Fronto-temporal Arcuate Fasciculus
AF_{FTP}	Fronto-temporo-parietal Arcuate Fasciculus
AF_{TP}	Temporo-parietal Arcuate Fasciculus
ANS	Approximate Number System
AS	Average arithmetic skills and experience
BOLD	Blood Oxygenation Level Dependent
CC	Corpus Callosum
CSF	Cerebrospinal fluid
DD	Developmental Dyscalculia
DMN	Default Mode Network
DTI	Diffusion Tensor Imaging
DWI	Diffusion-Weighted Imaging
EPI	Echo-planar image
FA	Fractional Anisotropy
fcMRI	Functional connectivity MRI
FDR	False Discovery Rate
FG	Fusiform Gyrus
fMRI	Functional Magnetic Resonance Imaging
FWE	Family Wise Error
FWHM	Full-width at half maximum
GLM	General Linear Model
HRF	Hemodynamic Response Function
HS	High arithmetic skills and experience
IFG	Inferior Frontal Gyrus
IFOF	Inferior Fronto-Occipital Fasciculus

ILF	Inferior Longitudinal Fasciculus
IOC	Inferior Occipital Cortex
IPL	Inferior Parietal Lobule
IPS	Intraparietal Sulcus
LPOCV	Leave-one-pair-out-cross-validation
M	Mean
MD	Mean Diffusivity
MRI	Magnetic Resonance Imaging
MVPA	Multivoxel Pattern Analysis
OECD	Organisation for Economic Co-operation and Development
PCC	Posterior Cingulate Cortex
PVC	Primary Visual Cortex
RD	Radial Diffusivity
RF	Radio Frequency
ROI	Region of Interest
SD	Standard deviation
SDT	Spherical Deconvolution Tractography
SFG	Superior Frontal Gyrus
SLA	Searchlight Analysis
SLF	Superior Longitudinal Fasciculus
SLF_1	Medial branch of SLF
SLF_2	Middle branch of SLF
SLF_3	Lateral branch of SLF
SPL	Superior Parietal Lobule
SVM	Support Vector Machine
TE	Echo time
TR	Repetition time
VBM	Voxel Based Morphometry

Overview of Doctoral Dissertation

"The advancement and perfection of mathematics are ultimately connected with the prosperity of the state."

– Napoleon Bonaparte

Motivation

Today's world requires us to process unprecedented levels of numerical information. Computers, smart phones, financial transactions, and healthcare information processing are just a few of the many contemporary demands requiring our numerical fluency. Numerical fluency is a major determinant of an individuals life quality, for example, numerical knowledge at age 7 predicts socio-economic status at age 42, even after controlling for the socio-economic status of the family into which the person was born, as well as the person's IQ, and reading achievement (Ritchie & Bates, 2013).

The necessity of this numerical fluency in our daily life therefore has serious consequences for those who are impaired in processing numbers. More specifically, low numeracy has been associated with life-long consequences for income (Estrada-Mejia et al., 2016), socio-economic status (Ritchie & Bates, 2013), medical decision making (Reyna et al., 2009), and even mortgage default (Gerardi et al., 2013). In the UK alone, the annual cost of low numeracy has been estimated to 2.8 billion Euros (Gross et al., 2009).
Furthermore, the Organisation for Economic Co-operation and Development (OECD) investigated how mathematical standards influences the economic performance in a nation. This study demonstrated that improving mathematical and science performance with 1.5 standard deviation improves the annual growth rates of GDP per capita with 0.87% (OECD, 2010).

Given the high relevance of numeracy for individuals' life quality and society in general, it is essential that we understand how numbers are processed in the human brain. Furthermore, we need to advance our general knowledge of the impaired neural processes correlated with number processing in individuals burdened with low numeracy. New insights uncovered by this research might influence how we

teach children the meaning of numbers, how the development of learning strategies for mathematics takes place, and how we can improve the effectiveness of interventions for low numeracy.

Objectives of this dissertation

The global objective of this dissertation is to progress our current knowledge of the neural correlates of number processing and impaired numeracy (i.e. Developmental Dyscalculia (DD)) by applying advanced neuroimaging techniques. The application of these advanced techniques will allow us to directly address following pending debates in the numerical cognition field.

- **Debate 1**: The main challenge when investigating basic number processing, is that one quantity can be presented in different formats: symbolic (e.g. "2") or non-symbolic (e.g. "♣♣"). To date, it is still debated how these different formats are linked to each other at a neural level. Either there is a neural representation of number independent of the format it is presented in (e.g. "2" and "♣♣" activate the same neurons representing the quantity two). Or, symbolic and non-symbolic numbers are processed differently in the human brain.

- **Debate 2**: Two theories of the etiology of DD have been proposed in the last decade. One theory suggests that the neural (symbolic and/or non-symbolic) number representations are impaired in DD. On the other hand, another theory proposed that the access to these neural number representations is impaired.

- **Debate 3**: Currently it is debated how number processing and arithmetic skills are intertwined. Some studies have found that both symbolic and non-symbolic number processing relates to arithmetic skills, while others only found an association between symbolic number processing and arithmetic skills.

This results in the following research goals of this dissertation:

- **Objective 1**: In this dissertation, we have used advanced neuroimaging analyses, such as Multivoxel Pattern Analysis (MVPA), to directly investigate how symbolic and non-symbolic numbers are processed and if their representations are overlapping in the adult brain.

- **Objective 2**: To tackle the neural etiology of DD, we applied a wide range of neuroimaging techniques to investigate both functional and connectivity correlates of DD in adults.

- **Objective 3**: By means of MVPA, we investigated how symbolic and non-symbolic number processing relate to arithmetic achievement in adults.

Chapter-by-chapter overview

The structure of this dissertation consists out of five parts each containing one or more chapters. The structure of this dissertation and the association between the chapters are outlined in Figure 0.1 and can be summarized as described below. In short, this dissertation comprises six studies that demonstrate the strength of applying advanced neuroimaging techniques to the numerical cognition field, each described separately in the Chapters 3 to 8.

Part I. General Introduction

This first part serves as an introduction into the numerical cognition field and the applied methods in this dissertation.

Chapter 1 presents a general introduction to the field of numerical cognition. Several theories about number processing and the etiology of DD, and their behavioral and neuroimaging evidence are discussed.

Figure 0.1: Structure of the dissertation.

Chapter 2 includes an overview of the advanced neuroimaging techniques applied in this dissertation. It presents an introduction about the method Magnetic Resonance Imaging (MRI) allowing us to study the anatomy and function of brain regions. Furthermore, the advantages and disadvantages of the analysis techniques for functional Magnetic Resonance Imaging (fMRI) data applied in this dissertation will be explained. Finally, the different methods used in this thesis to investigate the structural and functional connectivity in the brain are discussed.

Chapter 3 demonstrates the drawback of a restricted focus on only one Region of Interest (ROI), lobe, or the mere application of Searchlight Analysis (SLA) when MVPA is applied in a fMRI study. Via the use of simulated and real neuroimaging data, we demonstrated the necessity of incorporating different spatial scales in MVPA to draw conclusions on how neural representations are distributed across the brain. The proposed method allows one to discover useful information that can easily be overlooked when just a single MVPA method is used.

Part II. Association between symbolic and non-symbolic number representations

The second part of this thesis describes how the neural representations of Arabic digits and dots are intertwined in the human cortex. First, the degree of overlap between formats is investigated by directly examining the representations at different spatial scales in the entire human cortex (Chapter 4). Second, the exact nature of the association between both formats in the parietal cortex is revealed (Chapter 5).

Chapter 4 includes a study in which we investigated the possible overlap of Arabic digits and dots on three different spatial scales (entire lobules, smaller regions, and a searchlight analysis). Although there were distinct neural representations for different numbers in different occipital, temporal, frontal, and parietal regions for both formats, we found no evidence for overlapping representations of symbolic and non-symbolic numbers, on any spatial scale. Furthermore, we showed that repres-

entations of dots and Arabic digits are not restricted to the Intraparietal Sulcus (IPS) or the parietal cortex. The contribution of this study is that by applying MVPA fMRI, we (a) demonstrated the lack of abstract number representations in the IPS, parietal cortex, or anywhere in the human cortex and (b) that the neural process for symbolic and non-symbolic number encompasses different brain regions on different spatial scales.

Chapter 5 further extended the findings of Chapter 4. In Chapter 4 we found no evidence in favor of an abstract number representation in the human cortex. However, other neuroimaging studies have found similar activation patterns for symbolic and non-symbolic numbers in the parietal cortex. The contribution of this chapter is that we showed that there was an association between dots and Arabic digits at the neural level, but that this relationship was by the number of objects that are presented and not by the number they represented.

Part III. Neural markers of dyscalculia

The third part consists of studies investigating the etiology of DD. Two theories have been put forward to explain the numerical difficulties in this learning disorder. One theory postulates that symbolic and/or non-symbolic number representations are impaired in DD (Chapter 6). On the other hand, evidence in children with DD has demonstrated impaired connectivity (functional and structural) to brain regions related to number processing and number representations (Chapter 7).

Chapter 6 applied MVPA fMRI to directly compare the quality of symbolic and non-symbolic number representations in adults with and without DD. Our findings revealed that adults with DD have less precise non-symbolic magnitude representations at the neural level. These impaired representations were observed not only in parietal, but also in temporal and frontal regions. The contribution of this chapter is that we demonstrated that adults with DD have less precise magnitude representations in multiple brain regions.

Chapter 7 applied functional connectivity MRI (fcMRI), Diffusion-Weighted Imaging (DWI), and Voxel Based Morphometry (VBM) to investigate if the connectivity between number processing related brain regions and the anatomical structures are impaired in adults with DD. We found increased functional connectivity in temporo-occipital areas and increased grey matter density in the posterior cingulate cortex. The contribution of this chapter is that we demonstrated that impairments in DD are not limited to altered function of brain regions related to number processing.

Part IV. Arithmetic skills' and number processing

Chapter 8 investigated how arithmetic skills and experience relate to the degree of overlap in symbolic and non-symbolic numbers. Throughout our studies, we noticed an interesting variation in the degree of overlap between symbolic and non-symbolic numbers that seemed to be related to arithmetic skills and experience. In this short chapter, we explicitly tested the hypothesis that with increased arithmetic skills, the neural overlap between symbolic and non-symbolic number representations decreases. This finding fits the estrangement account of numerical cognition. The contribution of this chapter is that we demonstrated how the neural coupling between Arabic digits and dots can vary depending on the level of arithmetic skills and experience.

Part V. General conclusions and perspectives

Finally, chapter 9 of this work summarizes the main contributions and conclusions of the previous chapters and formulates suggestions for further research.

Part I

General Introduction

1 Processing numbers in the human cortex

"It is a good morning exercise for a research scientist to discard a pet hypothesis every day before breakfast. It keeps him young. "

– Konrad Lorenz

1

Overview

This chapter discusses the different ongoing debates regarding the nature of number representations in the human cortex, the neural correlates of DD, and how individual differences are related to number representations. An overview of this chapter can be found in Figure 1.1.

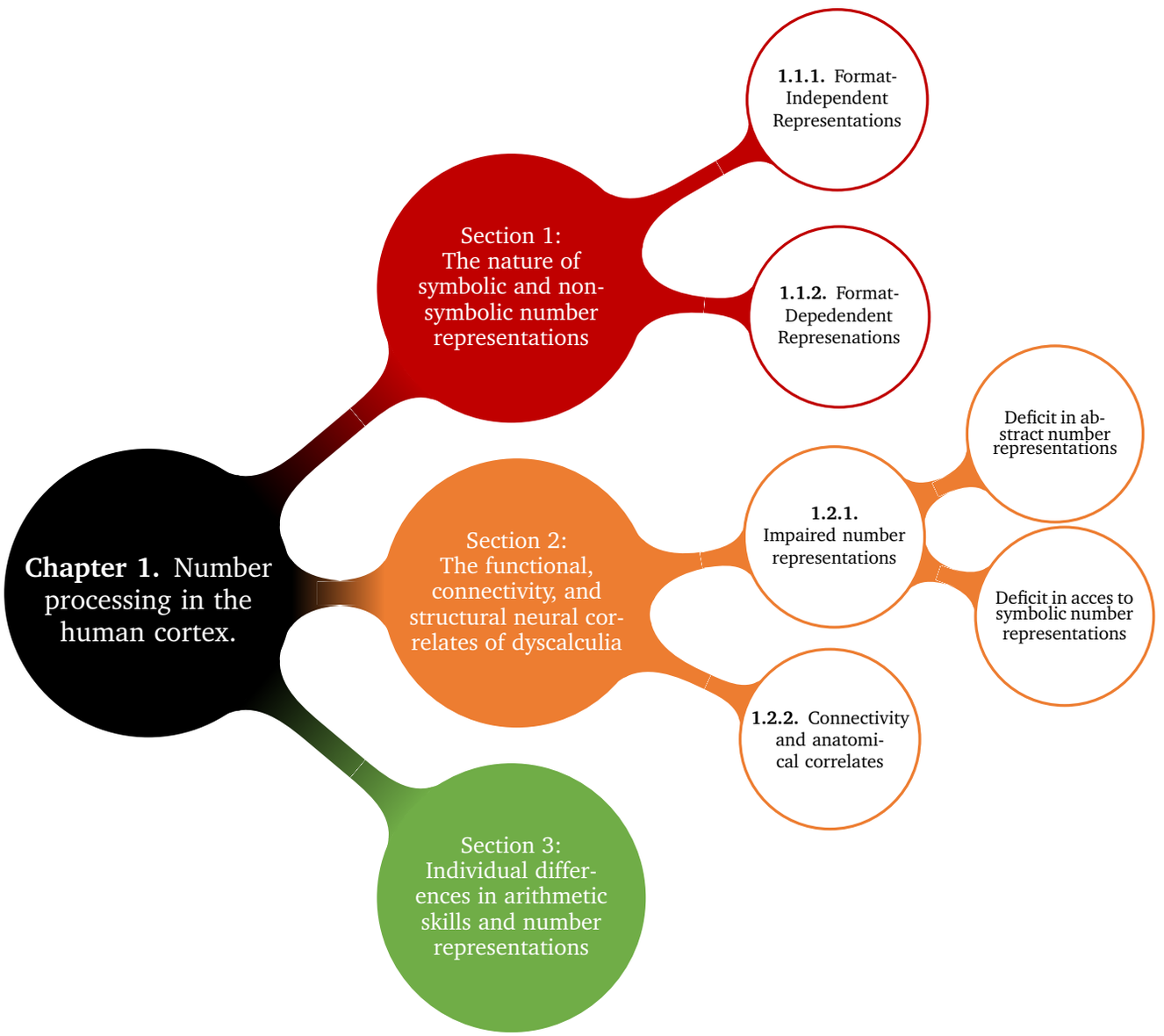

Figure 1.1: Structure of this chapter.

1.1 The nature of symbolic and non-symbolic number representations

Numbers can come in many forms. The same quantity can be represented by “two” (word), 2 (Arabic digit), ▲▲ (non-symbolic number), two fingers, temporal series (e.g. two drum beats), and even with other words (pair, duo). The question is how we represent numbers and whether there is an unitary neuronal basis for all forms of numerical representation (Cohen Kadosh & Walsh, 2009b).

A full understanding of numerical representations and the relation between symbolic and non-symbolic number representations is important for educational interventions, for diagnosis, classification, and the design of effective rehabilitation programs for people who show numerical difficulties, such as individuals with DD. For example, the way some intervention programs for DD are developed is based on the idea of an unitary neuronal basis for different forms of numbers (Wilson et al., 2006): it is assumed that training on non-symbolic numbers will improve the numerical computation with Arabic digits.

To date, there exists an intensive debate in numerical cognition about whether or not there is an abstract/unitary neuronal basis for different formats of numbers (for extensive discussion, see Cohen Kadosh & Walsh (2009b)). For the remaining part of this section, we will discuss these opposing theories and their (contra) evidence concerning the neural link between symbolic and non-symbolic number representations. Furthermore, we will explain how this dissertation will advance the current state-of-the-art of this debate by applying advanced neuroimaging techniques.

1.1.1 Format-independent number representations

One of the most prominent theories in the field of numerical cognition suggests that the ability to process non-symbolic numerical quantities is a basic, automatic, and innate ability that can be found across species. In other words, babies are born with

an analog magnitude system specifically tuned to numerical information, called the Approximate Number System (ANS) (F. Xu & Spelke, 2000; Lipton & Spelke, 2003; F. Xu, 2003; Feigenson et al., 2004; F. Xu et al., 2005).

When children learn the number words and the Arabic digits, these symbols take their meaning from the ANS and therefore a mapping emerges between symbolic and non-symbolic number representations (Dehaene, 1992; Dehaene & Akhavein, 1995; Piazza et al., 2010). Consequently, an abstract neural representation of numbers is developed which represents quantity regardless of whether the input notation is symbolic or non-symbolic Dehaene et al. (1998). This means that neuronal populations code for numerical quantity itself and are not influenced by the form of input in which the numerical information was presented (Cohen Kadosh & Walsh, 2009b). This idea is known as the format-independent or the abstract number representations theory.

Behavioral evidence

There has been a longstanding behavioral tradition in attempting to reveal the common representation of different numerical formats (Barth et al., 2003; Buckley & Gillman, 1974; Dehaene & Akhavein, 1995; Jaffe-Katz et al., 1989; Naccache & Dehaene, 2001; Shepard et al., 1975). One of the most important findings is the so-called numerical distance effect (Moyer & Landauer, 1967) that seems to be similar for symbolic and non-symbolic stimuli, which suggests a common numerical magnitude system for different formats (Dehaene et al., 1990). The numerical distance effect is the observation that reaction times increases and accuracy rates decreases in number comparison tasks when numerical magnitudes are closer in distance than when they are further apart. This effect has been observed in children (Feigenson et al., 2004; Lonnemann et al., 2011; Holloway & Ansari, 2009; Sekuler & Mierkiewicz, 1977), adults (Dehaene et al., 1990; Dehaene, 1992; Moyer & Bayer, 1976) and animals (Brannon et al., 2001; Nieder & Miller, 2003), and it has been contended that this indicates a similar way of representing numerical magnitudes across different species and ages.

Furthermore, it seems that the spatial numerical association of response codes (SNARC) effect is independent of notantion or modality as well (Nuerk et al., 2005). The SNARC effect is the observation that participants respond more quickly to small numbers with left-hand key responses than with right-hand key responses, and faster to large numbers with the right-hand key than with the left-hand key (e.g., responding to digit 3 will be faster with the left-hand key, whereas responding to digit 8 will be faster with the right-hand key) (Dehaene et al., 1993; Fias & Fischer, 2005; Gevers & Lammertyn, 2005; Wood et al., 2008).

Neuroimaging evidence

Extrapolating the idea of abstractness from above behavioral evidence to neural activity implies that within the IPS, the area most associated with numerical representation (see Cohen Kadosh & Walsh (2009b) and Dehaene et al. (2003) for reviews and meta- analyses), the same neural population will be recruited to encode numerical quantity, whatever the format of presentation.

Results of neuroimaging studies have found three main findings in favor of the format-independent number representations theory: (a) the IPS is involved in magnitude processing in humans (for extensive reviews see Ansari (2008); Nieder & Dehaene (2009)) and primates (Nieder et al., 2002; Nieder & Miller, 2003; Sawamura et al., 2002); (b) the amount of IPS activity correlates with the distance effect(Ansari, Dhital & Siong, 2006; Cohen Kadosh et al., 2005; Piazza et al., 2007; Pinel et al., 2004); and (c) the IPS activity does not differ between formats in humans (Eger et al., 2003; Fias et al., 2003; Piazza et al., 2007).

Deep learning networks have provided us as well with evidence for the abstract notion of number representations. Stoianov & Zorzi (2012) used deep learning networks with two hidden layers that were trained to reproduce the input numerosities. After training, some units in the second hidden layers demonstrated a response that

was unaffected by nonnumerical features such as size or densitiy of the input images.

Together these findings, both at the behavioral and the neuronal level, provide an apparently strong basis for the abstract representation of numbers. However, there are several limitations to this view, these will be discussed in the following section together with an alternative theory for neural number representations.

1.1.2 Format-dependent number processing

The existence of format-independent number representations has been questioned by several studies that demonstrated unidentical behavioral characteristics of symbolic and non-symbolic processing and moreover, that the neuronal populations that code for digit 2 or the two dots are not the same neuronal populations (for review, see Cohen Kadosh & Walsh (2009b)). The resulting hypothesis is known as the format-dependent number processing theory.

According to this theory, we do not map symbolic numbers onto the ANS, but we acquire a new numerical representation system, the exact number system, where we learn the meaning of symbolic numbers through order associations with other symbols (Carey, 2009; Noël & Rousselle, 2011; Sasanguie et al., 2017; Reynvoet & Sasanguie, 2016). More concretely, children will first gradually learn the meaning of the number *one*, some time later the number *two*, and so forth. Second, the child has to discover that the cardinal value of a number word is determined by its order on the list, and that successive numbers are related by the function "+1": For any known number n in the list, the value of the next number is $n+1$ (Noël & Rousselle, 2011). Once children have created this exact number system, they will start to link it with the ANS (Le Corre & Carey, 2007) which causes an increase in the ANS precision (Halberda et al., 2008).

In the remainder of this section, we will discuss behavioral and neuroimaging evidence in favor of this format-dependent number representations theory.

Behavioral evidence

Some behavioral observations are very difficult to reconcile with the abstract view on number representations (for extensive discussion, see Cohen Kadosh & Walsh (2009b) and De Smedt et al. (2013)). Lyons et al. (2012) found that comparing numerical magnitudes across formats is more difficult than comparisons within one format, suggesting that additional processing is required for cross-format comparisons. The experiments of Maloney et al. (2010) demonstrated that the distance effect of non-symbolic magnitudes is not correlated with that of symbolic magnitudes. Furthermore, children with DD are more impaired in symbolic tasks compared to non-symbolic tasks (De Smedt & Gilmore, 2011; Iuculano et al., 2008; Landerl & Kölle, 2009; Rousselle & Noël, 2007; Vanbinst & De Smedt, 2016). Moreover, Sasanguie et al. (2017) demonstrated with an audio-visual matching paradigm the existence of two different systems for processing magnitudes, i.e. an exact symbolic system, and an approximate non-symbolic system. Finally, a review by De Smedt et al. (2013) indicated that, in typically developing children, measures of symbolic but not non-symbolic number processing, are reliable predictors of individual differences in mathematics achievement (De Smedt et al., 2013). In sum, these behavioral data are difficult to reconcile with an abstract representation of numerical magnitudes.

Neuroimaging evidence

In addition to the behavioral evidence against the existence of a format-independent number representations, there has been a couple of patient and neuroimaging studies further challenging this theory. A study on patients with damage to the left supramarginal gyrus showed a dissociation between the processing of symbolic and non-symbolic magnitudes (Polk et al., 2001). Neuroimaging studies have demonstrated that the IPS contains an abstract representation of numerical order rather than numerical magnitude (Fias et al., 2007; Ischebeck et al., 2008) and that activity in the IPS while performing a numerical task was related to response-selection rather than numerical processing per se (Cappelletti et al., 2010; Göbel et al., 2004). Cohen Kadosh et al. (2011) did not observe cross-notation adaptation from non-symbolic to

symbolic number. Lyons et al. (2015) correlated, by applying representational similarity analysis, the activity patterns of two formats presenting the same number and found no evidence for shared neural representations in the IPS. They concluded (Lyons et al. (2015), p12): "IPS activity is thus sensitive to numerosity regardless of format; however, the nature in which symbolic and non-symbolic numbers are encoded is fundamentally different."

1.1.3 Objective 1 of this dissertation

The first objective of this dissertation, is to further investigate whether or not numerical magnitudes are processed in an abstract way in the human cortex by applying advanced neuroimaging analyses. One of the main issues in this debate is the fact that most evidence for an abstract representation of numerical magnitudes is based on null results, indicating no differences across formats in activation in the IPS (for overview, see Cohen Kadosh & Walsh (2009b)). It is crucial to point out that these null results emerge from fMRI studies that have used univariate methods to measure the overall regional activity for different conditions. Such data, however, limit our understanding of the information encoded by neural populations in that region. Therefore, it has been suggested that the application of MVPA to fMRI might be one way to solve this issue (Ansari, 2008; Cohen Kadosh & Walsh, 2009b; Dehaene, 2009).

Chapter 4 and 5 of this dissertation applied these advanced neuroimaging analyses to investigate if numbers in different formats have an abstract neural fingerprint. More information about these analyses can be found in chapter 2.

1.2 The functional, connectivity, and structural neural correlates of dyscalculia

Developmental dyscalculia (DD) is characterized by persistent deficits in arithmetic, with scores significantly below the population mean for age. This severe learning disability in arithmetic is present despite the absence of intellectual disabilities, visual,

auditory or motor impairments, adequate schooling, targeted remediation, or global developmental delays (e.g., other neurodevelopmental disorders) (American Psychiatric Association, 2013).

Although DD has a relative high prevalence, about 5-7%, the proportion of research dedicated to investigating the neural markers of DD is relatively low, especially compared to other neurodevelopmental disorders with the same prevalence (Dyslexia, Attention Deficit Hyperactivity Disorder) or even lower prevalence (Autism Spectrum Disorder) (Bishop, 2010; Butterworth et al., 2011). For example, during the period of 1985-2006 nearly 5 times as many research papers were published on dyslexia compared to dyscalculia (Murphy et al., 2007).

For the remainder of this section, we will discuss the neural correlates that have been associated with DD. The first part looks into deficits in neural number representations as association to DD. There, two opposing hypotheses have been put forward: on the one hand, DD could be associated with a deficit in abstract number representations (Ansari, 2008; Butterworth et al., 2011). Others suggested that DD is caused by impaired symbolic number representations (Rousselle & Noël, 2007; De Smedt et al., 2013). The second part gives an overview of the evidence of connectivity and anatomical deficits correlated with DD.

1.2.1 Impaired number representations

Impaired abstract number representations

The deficient number module theory suggests that DD is related to impairment of both symbolic and non-symbolic number representations in the IPS (Butterworth, 2010). According to this theory, humans are born with an innate ANS and DD occurs when this basic ability to process numbers fails to develop normally, resulting in difficulties to understand number concepts (e.g., Arabic digits). Note that this theory implicitly implies a format-independent account for number representations and thus suggests that there should be *observable deficits in both* symbolic and non-symbolic

number processing.

There have been couple of studies demonstrating overall impairments in both symbolic and non-symbolic number processing in DD, confirming latter hypothesis: neuroimaging studies observed altered activation in the IPS in children with DD during number comparison task of non-symbolic numbers (Mussolin et al., 2010; Price et al., 2007) and symbolic numbers (Mussolin et al., 2010). These differences in brain activity suggest an inappropriate task-modulation of the IPS during number processing of both digits and dots in DD, however they did not directly provide any information about the quality of the involved representations.

Impaired exact number representations

According to the, above explained, impaired abstract number representations account for DD, there should be deficits in *both* symbolic and non-symbolic number processing. However, several behavioral studies failed to find a deficit in non-symbolic number processing in children with DD, in contrast to a clear deficit in symbolic number processing (Rousselle & Noël, 2007; Iuculano et al., 2008; Landerl & Kölle, 2009; De Smedt & Gilmore, 2011).

Therefore, (Rousselle & Noël, 2007; Noël & Rousselle, 2011) proposed that the central deficit in DD is not a defect ANS (and therefore, an incapability to sufficiently acquire the meaning of digits), but rather a deficit in the *separate* neural representations of symbolic numbers (i.e. the exact number system). The non-symbolic number deficit in older children with DD can be explained by the fact that when children with DD start to link their separate "exact number representations" to the ANS, their deficit in this exact number system prevents them from refining their ANS in the same way as typically developing children do (Noël & Rousselle, 2011). This inefficient refinement would predict a slower growth of non-symbolic numbers in DD children. This delayed maturation of number acuity would lead to increasing difference in number acuity between DD and control children over development (De Smedt et al., 2013).

Interestingly, this account can therefore explain the contradictory results found in children with DD. It seems that studies who found impaired symbolic processing together with intact non-symbolic processing are in children aged between 6-9 years old (De Smedt et al., 2013). However, when older children (10 and over) were tested they showed differences in both symbolic and non-symbolic number processing (Mussolin et al., 2010; Price et al., 2007; Mazzocco et al., 2011).

1.2.2 Connectivity and anatomical correlates of dyscalculia

Besides the investigation into impaired symbolic and/or non-symbolic number representations, there has been also couple of studies investigating the neuroanatomical and (structural and functional) connectivity correlates of DD.

The study reported by Rykhlevskaia et al. (2009) demonstrated reduced grey matter in the superior parietal lobule, IPS, fusiform gyrus, parahippocampal gyrus, and the right anterior temporal cortex in children with DD. In addition, white matter volume in the right temporal parietal cortex was reduced. Moreover, they observed abnormalities in the right hemisphere temporal-parietal white matter and associated pathways (i.e., the Inferior Fronto-Occipital Fasciculus (IFOF) and the Inferior Longitudinal Fasciculus (ILF)) in DD. Another study, demonstrated hyper-connectivity between the IPS and lateral fronto-parietal regions, and between the IPS and the default mode network in children with DD (Rosenberg-Lee et al., 2015). Additional evidence of white matter abnormalities in DD comes from a study by Kucian et al. (2013), who suggested that DD may be related to poor connections between regions critical for mathematical processing, particularly in the Superior Longitudinal Fasciculus (SLF).

All of the aforementioned studies report at least some association between inferior parietal or temporo-parietal white matter and DD, in particular, the SLF, ILF, and the IFOF may be key tracts. The degree to which these white matter abnormalities are lateralized is unclear, partly due to the great variability of the populations and

methods used in these studies. Overall, these studies demonstrate that deficits in arithmetic are not just due to atypical brain function, but also due to atypical brain structure and connectivity (Matejko & Ansari, 2014).

1.2.3 Objective 2 of this dissertation

The second objective of this dissertation is to investigate the neural basis of DD focusing upon many of the potential factors, including atypical number representations, atypical brain structure and connectivity using state-of-the-art neuroimaging techniques. In chapter 6 of this dissertation, we directly investigated if the neural representations of symbolic and/or non-symbolic numbers are impaired in adults with DD by applying MVPA. In chapter 7, we applied a wide variety of neuroimaging techniques to unravel structural and functional connectivity abnormalities in adults with DD. More information about these analyses can be found in chapter 2.

1.3 Individual differences in arithmetic skills and number representations

When it comes to arithmetic skills, there is enormous variations between individuals. Based on the above mentioned theories, one can speculate about how these variations in arithmetic skills are linked to the way we learn the meaning of symbolic numbers. One theory states that we map the symbolic numbers onto the ANS (Dehaene et al., 2003; Feigenson et al., 2004), while the other one claims that we first acquire an exact number system which is then linked to the ANS (Carey, 2001). Either way, the link between symbolic and non-symbolic numbers is made throughout development. At least according to these theories.

On the other hand, Lyons et al. (2012) suggested another theory that specifically expects a relationship between the *overlap* of neural representations between non-symbolic and symbolic numbers and *arithmetic skills*. According to this estrangement theory, symbolic representations acquire their meaning through the mapping of a

number onto the ANS, however, over the course of development and with increasing arithmetic skills these symbols become "estranged" from the non-symbolic representation. Thus, this account predicts that the better the arithmetic skills, the higher the estrangement and thus the weaker the mapping between symbolic and non-symbolic representations.

1.3.1 Objective 3 of this dissertation

The third objective of this dissertation consists of unraveling the relationship between arithmetic skills and the neural overlap between symbolic and non-symbolic numbers, with the means of MVPA.

1

2 Experimental Techniques

"It was basic research in the photoelectric field - in the photoelectric effect that would one day lead to solar panels. It was basic research in physics that would eventually produce the CAT scan. The calculations of today's GPS satellites are based on the equations that Einstein put to paper more than a century ago."

– Barack Obama, *National Academic of Sciences Meeting 2009*

2

2.1 Magnetic Resonance Imaging

During the last two decades, MRI has become the most dominant technique in the cognitive neuroscience. The reason for this, is that by the means of MRI scanners, neuroscientists are able to create images of the brain anatomy (i.e. MRI), detect activated brain regions (i.e. fMRI), and determine functional and structural connectivity between brain regions (i.e. fcMRI and DWI). And, most important, this can be done in a non-invasive manner for the participant. In this section, I will further explain how a MRI scanner accomplish this task.

2.1.1 It's all about physics

Humans are mostly made out of water (about 70%). Water consists of water molecules, which are made up of two hydrogen atoms and one oxygen atom. It is the energy released by these hydrogen atoms the MRI scanner can detect, however, in order to do this it needs to do "something" to the hydrogen atoms (Tilakaratna, 2012).

Each atom has a nucleus and a shell. The nucleus comprises protons, which are little particles that have a positive electrical charge. These protons are constantly orbiting around an axis (e.g. like our earth, for example), which is referred to in physics as spins, causing an electrical current. This electrical current induces a magnetic field. Thus, the proton in the nucleus (part of the hydrogen atoms) has its own magnetic field. Under normal conditions, these protons are oriented at random (Figure 2.1A).

When a person, consisting out of atoms, is exposed to an external magnetic field (i.e. the magnet of the scanner), the protons can align with this static magnetic field in two ways: in the complete opposite direction or parallel to the external magnetic field (Figure 2.1B). Both types of alignment have different energy levels, with parallel alignment taking the lowest amount of energy and consequently, that is their

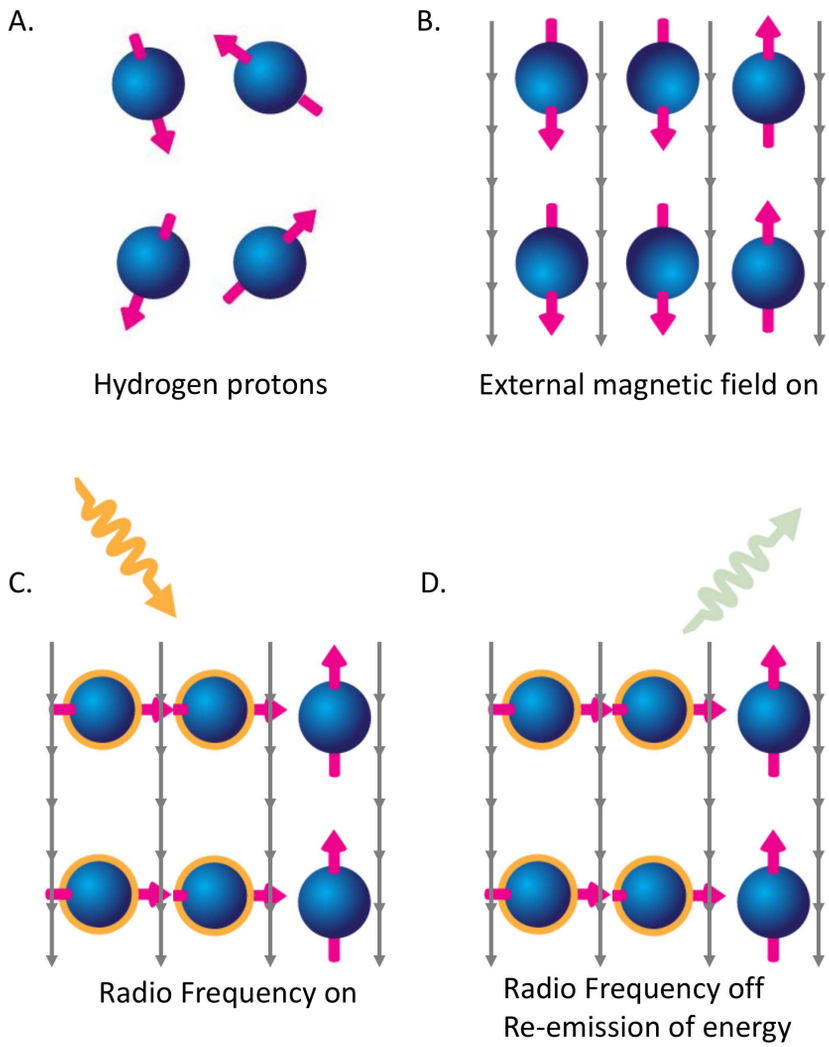

Figure 2.1: Overview of the sequence of events of protons subjected to external magnetic field and radio frequency. The blue dots represent the protons in the nucleus of an hydrogen atom. The red arrows represent the spinning direction of the protons. The grey arrows represent the external magnetic field. *A*. Randomly oriented protons in absence of an external magnetic field.; *B*. Protons align parallel or in opposite direction to the external magnetic field.; *C*. When a RF pulse is sent out, the protons in the parallel direction will absorb the energy from the RF pulse and switch direction.; *D*. When the RF pulse is stopped, the newly aligned protons will release the energy that was given to them by the RF pulse and go back to their previous alignment.

preferred state of alignment and therefore most protons will be aligned parallel to the magnetic field of the MRI scanner.

In the MRI scanner, we send out a Radio Frequency (RF) pulse, which will disturb the protons' alignment, making us able to detect them (Figure 2.1C). For the RF pulse to be able to do this, it must have the same frequency as the spinning protons (i.e. resonance frequency). The protons aligned parallel to the magnetic field (i.e. low en-

ergy protons) absorb the energy sent from the RF pulse. Because of that, they change their spin to the opposite direction of the magnetic field of the MRI scanner (transverse magnetization) and become high energy protons. After a short period, the RF signal is stopped, causing the new high energy protons to release the energy that was given to them and to go back to their previous low energy state (Figure 2.1D).

This release of energy by the protons are picked up by the receiver coil of the MRI scanner and can be described by two distinct time constants: T_1 and T_2. The T_1 relaxation time reflects how quickly the protons return back to their previous realignment with the magnetic field, namely in the low energy state. The T_2 constant describes how quickly the protons emit energy when recovering to equilibrium (spin-spin relaxation). Two factors contribute to the decay of transverse magnetization: molecular interactions and local inhomogeneity of the magnetic field (dephasing of spins). The signal loss caused by the combined effects of spin-spin relaxation and field inhomogeneity lead to signal loss known as T_2^* time constant ($T_2^* < T_2$).

2.1.2 Scanning the brain

Due to the association between the magnetic field of the scanner and resonant frequency, the MRI is able to detect the hydrogen protons in the brain. However, the scanner cannot simply scan the entire brain at once, as the signals returning from all parts of the brain at the same time would result in a messy signal.

Instead, the MRI machine scans the brain in sections (i.e. slices). For every slice, the process explained above is repeated and the head coil picks up the returning energy from the protons in that slice. Combining the information from these different slices enables the scanner to eventually construct an image.

An important issue is to ensure that the MRI machine makes sure that only hydrogen proton in the slice of interest respond, while all the other ones are kept quiet. There are gradient coils that alter the main magnetic field of the scanner, so that the

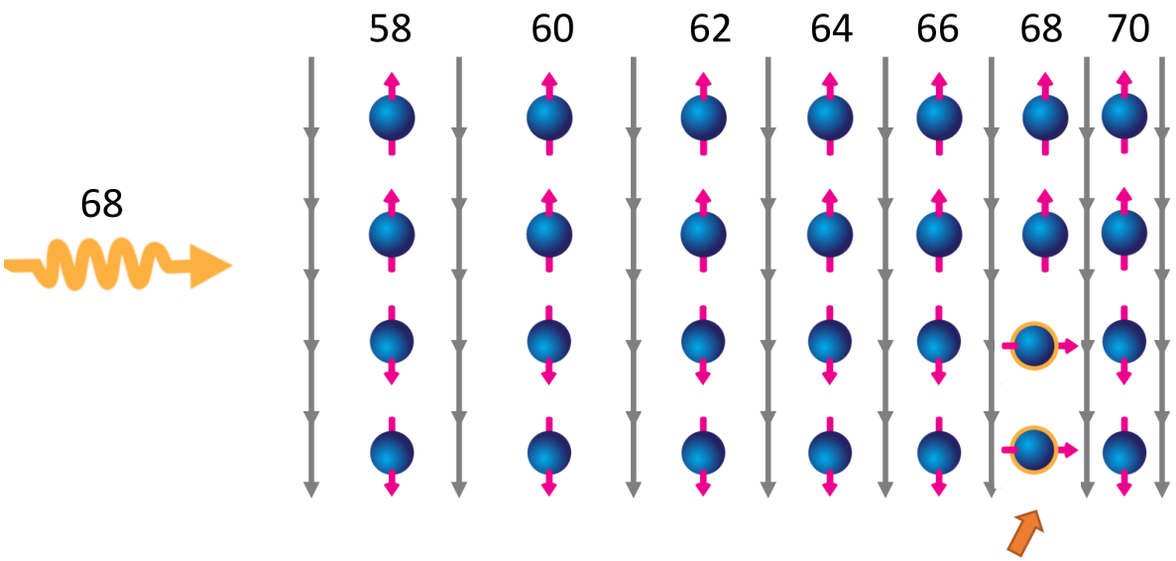

Figure 2.2: Overview of MRI acquisition. The blue dots represent the protons in the nucleus of an hydrogen atom. The red arrows represent the spinning direction of the protons. The black arrows represent the external magnetic field. The strength of the external magnetic field is not the same at all locations, because of a gradient coil resulting in a magnetic field gradually changing the magnetic field strength (represented by the closeness of the black arrows). The numbers represent the frequency (MHz) of the protons in that location of the magnetic field. The higher the strength of the magnetic field, the higher the resonant frequency. A RF pulse with a certain resonant frequency (MHz) is send out. Only the protons with the same frequency as the RF pulses frequency can absorb the energy of the RF pulse. Thus, only in that slice of the magnetic field the protons will change alignment.

magnetic field per slice differs (i.e. magnetic gradient) (Figure 2.2A). Therefore, the resonant frequency of the protons in different slices will differ (e.g. in slice 1 70 MHz, in slice 2 68 MHz, and so on). As mentioned above, protons can only pick up the energy send from the RF coil if it has the same frequency (Figure 2.2B). By changing the frequency emitted by the RF coil (e.g. 70, 68, 66, and so on), the MRI machine can look for hydrogen protons slice by slice in an orderly manner.

Furthermore, the returning signal is different for different tissues because grey matter contains more cell bodies (e.g. neurons and glial cells) than white matter, which primarily consists of long-nerve fibers.

Many pulse sequences are available, emphasizing different aspects of normal and abnormal brain tissue. The returning signal is different for different tissues because

grey matter contains more cell bodies (e.g. neurons and glial cells) than white matter, which primarily consists of long-nerve fibers. By modifying sequence parameters such as Repetition time (TR) and Echo time (TE), anatomical images can emphasize contrast between grey and white matter (e.g., T1 short TR and short TE). TR is the time interval between two successive RF pulses, usually expressed in seconds. TE is the time interval between the RF pulse and data acquisition, usually expressed in milliseconds. For example, an anatomical scan has a short TR and short TE and provides a good contrast between grey matter and white matter tissues, while Cerebrospinal fluid (CSF) is void of signal.

2.2 Revealing brain activation and neural representations

Above described techniques reveal the anatomy of the brain, however, they cannot address which brain regions are associated with which cognitive functions. To study the many functions of the brain, researchers apply another modification of the MRI scanner, known as fMRI.

2.2.1 The principles of functional neuroimaging

Our brain needs glucose and oxygen as fuel, however it cannot store these energy sources itself, it continuously retrieves them from blood. When brain regions become more activated by a task, the metabolic demands of the neurons increase in affected regions and consequently the blood supply to that region increases to meet the demand. This is called the hemodynamic response and peaks after 4 to 5 seconds after the onset of activation (Poldrack et al., 2011).

The oxygen in the blood is carried by hemoglobin. Hemoglobin carrying oxygen is referred to as oxygenated hemoglobin; once the oxygen has been emitted it is called deoxygenated hemoglobin. The essential difference, at least to pick up neural activations with fMRI, is that both types of hemoglobin differ in magnetic properties: oxy-

hemoglobin is diamagnetic, while deoxyhemoglobin has strong paramagnetic properties. The ratio between oxyhemoglobin and deoxyhemoglobin affects T_2^*: low ratio of deoxyhemoglobin/oxyhemoglobin causes a slow decrease in MRI signal, while a high ratio gives a fast decay in MRI signal. The changes in MRI signal can be measured using an appropriate MRI sequence: the Blood Oxygenation Level Dependent (BOLD) contrast. The change in the MRI signal caused by a neural event is typically referred to as the Hemodynamic Response Function (HRF).

The BOLD-signal is measured using rapid volumetric acquisition of T_2^*-weigthed images. The preferred imaging technique to acquire a BOLD-contrast is echo-planar image (EPI). EPI is the fastest acquisition method in MRI (100 ms / slice), because it sends out a single RF pulse first and then rapidly change spatial gradients. We used this acquisition method in chapters 3 - 8.

2.2.2 Data preprocessing

Researchers often use fMRI to relate specific processes to specific brain regions and networks in the brain. However, in order to achieve this, a long way paved with data analyses lies between acquiring the data with the MRI scanner and the actual activation maps (Poldrack et al., 2011). The first step in this analysis pipeline is the preprocessing of the fMRI data. The purpose of the preprocessing step is to attenuate noise and to correct for head motion.

Slice timing correction is done because the whole brain is usually not covered at once, but with a series of successively measured slices (see above). For a functional volume of 20 slices and a volume TR of 3 seconds, for example, the data of the last slice is acquired almost 3 seconds after the data of the first slice were collected. Despite the sluggishness of the hemodynamic response, an imprecise specification of time in the order of 3 seconds will lead to suboptimal statistical analyses. In this dissertation, we used temporal interpolation to solve this issue.

Furthermore, the quality of fMRI data is strongly hampered by the presence of head movements. Motion correction can be applied by selecting one functional volume of a run as a reference to which all other functional volumes of that run are aligned, this preprocessing step is called realignment. In this dissertation we aligned the volumes to the first image of the run. Furthermore, realignment is applied to correct for the movement of the head within and across scans. All the EPI volumes for a participant are realigned to the first image in the sequence.

Co-registration is then applied, which involves the spatial alignment of the mean EPI volume for each run (resulting from realignment) with the anatomical scan of that participant. This way, we can map functional information onto the anatomical space.

In order to perform whole-brain analyses with the data from multiple participants (group analyses), the data are normalized. This step involves transforming the data to a common, normalized space (e.g. Talairach or MNI space).

Finally, the normalized images are then convolved with a Gaussian smoothing kernel. Spatial smoothing means that data points are averaged with their neighbors. Smoothing leads to an increased signal-to-noise ratio and is justified by the fact that fMRI data inherently show spatial correlations due to functional similarities of adjacent brain regions. Furthermore, smoothing improves the validity of the further discussed statistical tests by making the error distribution more normal, which is one of the assumptions of the statistical tests applied for fMRI data. Another advantage of smoothing is the accommodation of anatomical and functional variations between subjects. Although coregistration and normalization is applied, there is still a substantial variation in individual brains as activated areas are rarely located in exactly the same voxels. A voxel is the unit of the 3-dimensional brain image, similar to a pixel for a photograph. Smoothing increases the overlap of activated brain regions across participants.

2.2.3 General linear model

Once the data is properly preprocessed, statistical methods are applied to estimate which brain regions show significant signal change in response to the different conditions of a task.

The General Linear Model (GLM) has become the core tool for fMRI data analyses after its introduction into the neuroimaging community by Friston, Holmes et al. (1994). The GLM predicts the variation of a dependent variable in terms of a linear combination of several independent variables. For fMRI, the dependent variable corresponds to the observed BOLD response of a voxel. The independent variables correspond to the time courses representing the presence of an experimental condition. The standard GLM equation, for i observations modeled using j predictor variables, is given by

$$y_i = \beta_1 x_{i1} + \beta_2 x_{i2} + \beta_3 x_{i3} + ... + \beta_j x_{ij} + \varepsilon_i$$

where y refers to the measured BOLD response from one voxel, x is an explanatory variable (e.g. experimental condition), ε is the Gaussian error for observation i, and β is a parameter estimate for predictor variable j.

In fMRI implementations of the GLM, the design matrix specifies how the explanatory variables change over time. It consists of a matrix with one row per time point in the experiment (i.e. each functional image) and one column per modeled experimental effect (i.e. condition). The contribution of each explanatory variable to the response variable is estimated using standard least squares, yielding a voxel-by-voxel image of the β-weights. This β-weights map reflects for each voxel how active that voxel was during that specific experimental condition.

In this dissertation, we applied the GLM to fMRI data in chapter 4, 5, 6, and 8 to estimate the activation for every voxel for every number (1, 2, 4, 6, 8) in each format

(Arabic digits and dots). Furthermore, motion parameters estimated during realignment are included as covariates. We opted to estimate the activation for every number in every format separately to be able to distinguish the activation patterns of these numbers by multivoxel pattern analysis in different ROIs.

2.2.4 Univariate Analyses

To address the question 'Which areas of the brain are significantly more activated when a person performs a given task?', univariate analyses are often applied to fMRI data. These analyses test at each voxel if an experimental condition (e.g. Arabic digits) has a higher activation compared to either the baseline brain activity (i.e. the observed signal changes can be explained purely by random variation in the data) or compared to another condition (e.g. fixation task). This comparison is called a contrast and basically, consists of subtracting the β-weights map of the, for example fixation task, from the β-weights map from the experimental condition.

There are two common approaches to apply univariate analysis: whole-brain approach or ROI-based approach. First, the whole-brain univariate approach will result in the localization of those regions showing increased activity for the experimental condition compared to, for example, a fixation task. To achieve this, the significance of a contrast is tested with a *t*-statistic applied at each voxel. As a statistical test is performed at each voxel and a scanned volume easily comprises over 100 000 voxels, about 5000 voxels should be significant due to chance alone (with $p < 0.05$). Therefore, correction for multiple comparisons needs to be applied to control for false-positive results. If this is not properly done, this could ironically result in activated brain regions even in a dead salmon (Bennet et al., 2009). The most common multiple comparison correction approach is to use information about spatial properties of activation, either through applying the Family Wise Error (FWE) or False Discovery Rate (FDR) to Random Fields (Worsley et al., 1996) or cluster-size thresholds (Friston, Worsley et al., 1994).

When the brain regions correlated with a specific task or experimental condition are already known in the literature, a researcher can opt to preselect the ROIs in which they want to investigate the activation levels. For that approach, the β-weights for each voxel in that ROI are averaged for each experimental condition separately (e.g. for Arabic digits and for fixation task) and then submitted to a two-sample *t*-test to assess significance. With multiple ROIs, a correction for multiple comparisons should be applied (i.e., FDR).

Both approaches result in knowing which regions are activated more compared to a base-line or another condition. In this dissertation we applied a whole-brain univariate analyses on the localizer data in chapter 4. In chapter 6 we applied both whole-brain and ROI-based univariate analyses on the experimental data.

2.2.5 Multivariate Analyses

Although univariate analyses are very good at revealing the brain regions that are selectively activated for specific mental functions, they are not able to detect more fine-grained representations within a ROI and thus can only pick up average activation changes (Figure 2.3).

Merely comparing the average activation between two conditions is particularly problematic for the format-independent number processing theory (see chapter 1). Evidence for the IPS as a number module mainly consists of finding no differences in the level of activation for different number formats (i.e. symbolic vs. non-symbolic numbers) (Cohen Kadosh & Walsh, 2009b). Therefore, the conclusion that numbers are abstract may be due to a lack of statistical power, or the insensitivity of the paradigms used.

Another way to unravel the overlap (of the lack thereof) between the representations of non-symbolic and symbolic numbers in the IPS and the distribution of local biases for particular types of comparison is by using MVPA (Norman et al., 2006; Peelen &

Downing, 2007). In this approach, data from individual voxels within a region are jointly analyzed, in contrast to traditional fMRI analysis that focuses on characterizing the relationship between cognitive variables and the *average* activity in a brain region. One of the biggest advantages of MVPA is that this method is sensitive to the different activation *patterns* of the compared conditions, even when individual voxels only give a very small indication about this distinction.

To the best of our knowledge, there have only been four recent studies that demonstrated the potential of MVPA to study number representations in parietal cortex (Damarla & Just, 2012; Eger et al., 2009; Raizada et al., 2010; Zorzi et al., 2011). These studies demonstrated that MVPA has the sensitivity that is required to investigate the nature of the numerical representations in the parietal cortex, but did not yet provide much insight into these number representations in the IPS or other cortical regeions.

This dissertation extends these previous findings by using MVPA fMRI to (a) look at the neural representations of numbers in different formats in brain regions in and beyond the parietal cortex, in order to investigate the full processing pathway from visual to number-sensitive representations (chapter 4); (b) challenge the theory of abstract representations of numbers and test an alternative hypothesis: that numbers are processed as visual units instead of abstract quantities (chapter 5); (c) investigate how numbers representations differ in individuals with impaired arithmetic skills (chapter 6); and (d) investigate how number representations of different formats are tied to individual differences in arithmetic skills and experience (chapter 8).

There are different MVPA approaches that one can apply, such as decoding MVPA or representational similarity analysis. For the remainder of this section, the applied MVPA approaches and the different included spatial scales in this dissertation will be explained.

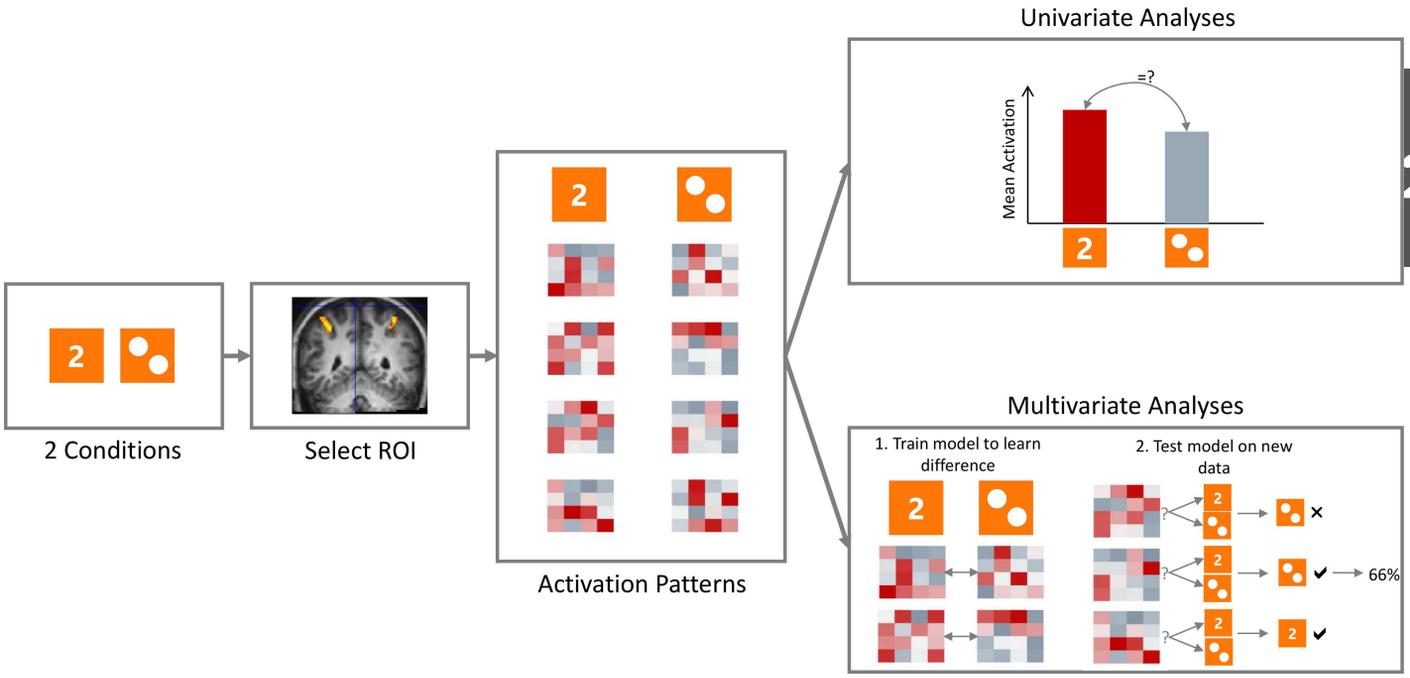

Figure 2.3: Comparison of Univariate Analysis versus MVPA.

MVPA Approaches

Decoding MVPA Figure 2.3 intuitively demonstrates what MVPA is and how it is different from univariate fMRI analyses. In the example, there are two experimental conditions with each four trials: Arabic digit 2 and 2 dots. Subsequently, a ROI (e.g., IPS) is selected, with in this example 16 voxels. The activation patterns for each trial can be extracted in this ROI.

Univariate analyses average across the activation of those 16 voxels and thereby ignores the activation "pattern" across the voxels that might be unique for that experimental condition. For example, the left voxel of the lowest row, is always very activated for Arabic digit 2, while almost always less activated for 2 dots.

On the other hand, with MVPA you first train a model to learn to distinguish both conditions based on these activation patterns. The model might pick up on that voxel in the left lower corner that distinguishes easily between both conditions and it gives a higher weight. Once the model is sufficiently trained, we test with new data/trials

that the model has never seen before.

The model then predicts for each new activation pattern what the presented experimental condition was that elicited this activation pattern. The overall accuracy of the model can subsequently be calculated. If the model scores above chance level (50%), then both conditions elicit distinguishable neural representations in that ROI.

In chapter 3-6 and 8, we made use of a linear Support Vector Machine (SVM) classifier for MVPA. SVMs have become the method of choice to solve difficult classification problems in a wide range of neuroscience domains (for an overview, see Lewis-Peacock & Norman (2014)). What makes these classifiers so popular? Their fame mainly rests on the fact that they can handle high-dimensional data combined with a small set of training patterns. This is very relevant for fMRI applications since we typically have many features (voxels), but only a relatively small set of trials per class. While this SVM property is useful to reduce the "curse of dimensionality" problem by reducing the risk of over-fitting the training data, it is still important to reduce the number of voxels as much as possible. In machine learning, this feature reduction step is referred to as feature selection. One way of selecting features consists in restricting the number of voxels to the ones in anatomically or functionally defined ROIs, which was done in the studies in the dissertation.

Generalization MVPA Another advantage of decoding MVPA, is that one could train on different conditions than the test conditions. An example of this analysis is given in Figure 2.4. There are four conditions in a 2×2 design: two numerosities and two formats. For each of the conditions there are a couple of activation patterns available. In the train phase, the model learns to distinguish between two numerosities in the same format (e.g., one versus two dots). In the test phase, the model is fed with new data from new conditions: the same numerosities, but different format (e.g. digit 1 versus digit 2). If the ROI contains neural representations that are invariant of format, than the classifier should be able to correctly classify digit 1 and digit 2, and thus performing above chance level.

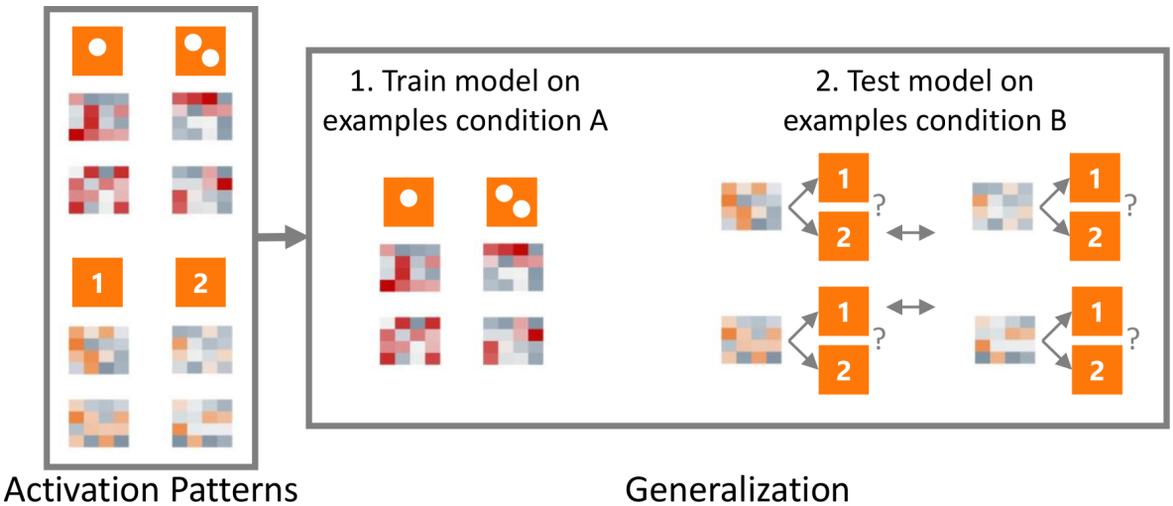

Figure 2.4: Example of MVPA Generalization.

For numerical cognition, this analysis is exactly what is needed to test the format-independent number processing hypothesis (chapter 1). Previous applied univariate analyses predict a *non-significant* difference in activation for this hypothesis, namely *no significant difference* in activation elicited in IPS by symbolic and non-symbolic numerosities. When generalization MVPA is applied to test the format-independent hypothesis and if there are format-invariant representations for number, the model should be able to correctly classify the test conditions and therefore reach *significant* generalization accuracies as evidence for the hypothesis.

We applied this analysis in chapter 4 and 8 to obtain a measure of the level of overlap of neural representations between Arabic digits and dots.

Subject Classification Instead of decoding different conditions within one subject, it is possible to decode between the functional data of participants from two groups (Ung et al., 2014). In other words, can we differentiate between the two groups based on functional activity?

In Figure 2.5 the procedure of this analysis is shown. First, the functional contrasts 'symbolic numbers minus fixation' and 'non-symbolic numbers minus fixation' from

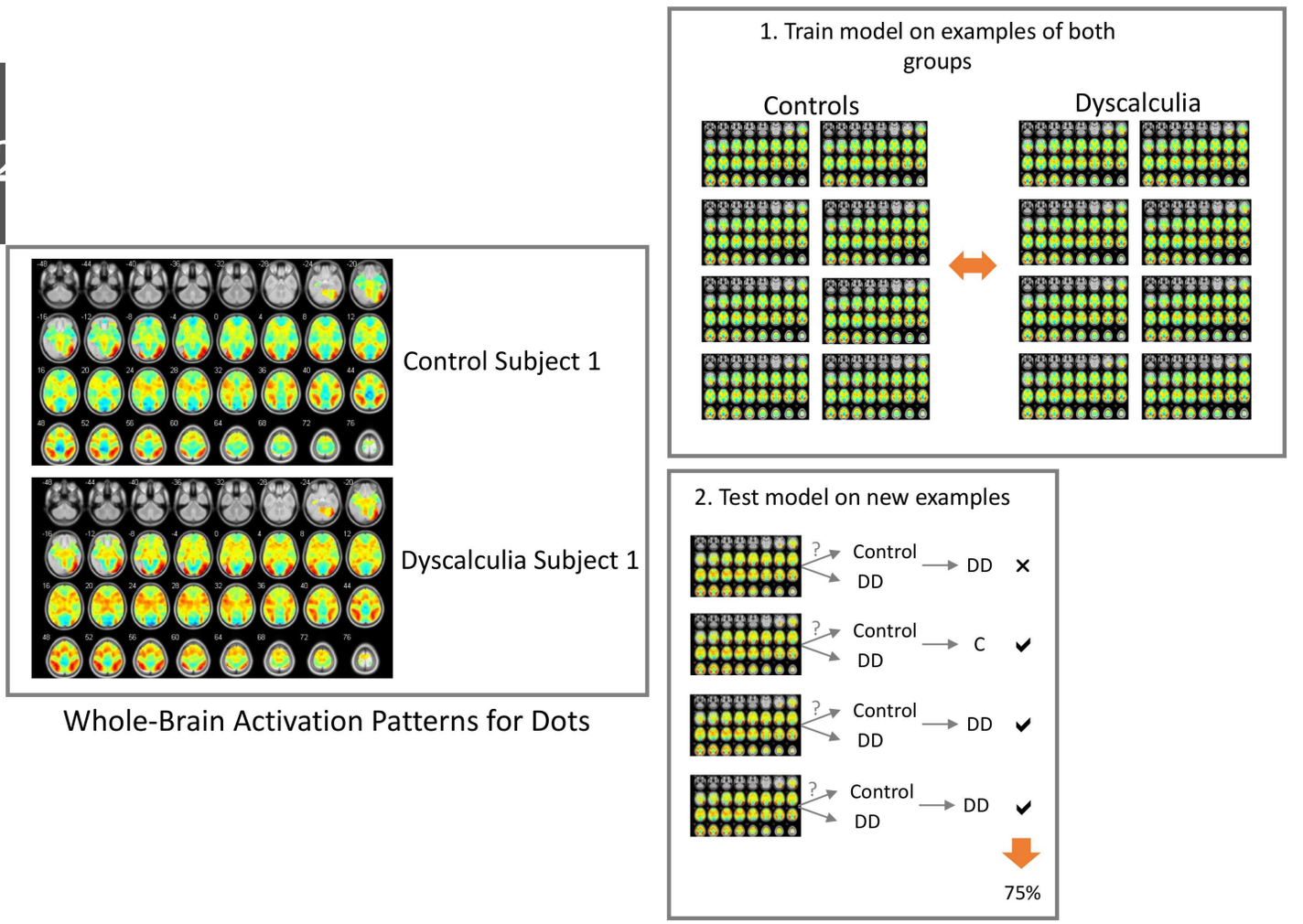

Figure 2.5: Example of MVPA Subject Classification.

the experimental runs for every participant are taken. In the training phase, the model learns to distinguish between the whole brain activation maps of two groups of participants on one condition. In the test phase, the model will have to predict for new activation maps of participant to which group it belongs. If the classifier can do this above chance level, it means that there are distinguishable activation patterns on a whole-brain level between the two groups.

It is important to point out that this analysis does not uncover the underlying differences in the quality of the neural representations of symbolic numbers and non-symbolic numbers between the groups, but tests if there is a more general difference in activation between the two groups when symbolic and non-symbolic numbers are

processed. In this way, this analysis is more closely related to a second level univariate analysis than to multivariate ROI-based decoding and searchlight analysis. The main difference with a second level univariate analysis lies in the fact that there is no activity-based comparison at the level of single voxels, but a spatial pattern comparison between the two groups across the whole brain or within a selected ROI. We applied this subject classification analysis in chapter 6.

Spatial scales

With univariate analyses, one can follow either a whole-brain or ROI-based analysis. MVPA offers the same possibilities, but depending on the spatial scale level selected, different properties of the neural representations are revealed. In chapter 3, we showed the necessity of including several spatial scales when investigating the neural representations of a certain condition.

In this dissertation, we made use of the combination of all of these spatial scales: whole-brain (or the "All Regions" ROI), lobes, ROIs (e.g., IPS), and searchlight analysis. We used them in a hierarchical order, meaning that we first tested if there is an effect at the "All Regions" level. If so, we further localized this effect to the lobes. Within the lobes demonstrating a significant effect, we investigated the effect further in pre-defined ROIs to pinpoint the precise locus of the representations of the experimental condition within smaller brain areas. This way, we can determine the spatial distribution of the neural representations of the conditions of interest.

To correct for multiple comparisons, we corrected with the FDR correction within all four lobes and within the ROIs of one lobe. This reasoning is similar to the well-known statistical approach of only testing a priori *t*-contrasts (e.g., pairwise comparisons) if an *F*-test including all conditions shows significance.

Afterwards, we applied a SLA to further investigate the local spatial activity patterns of different conditions without selecting any ROIs. This method is particularly suited

for uncovering where in the brain the local spatial activity pattern differs across conditions (Kriegeskorte et al., 2006; Kriegeskorte & Bandettini, 2007). These analyses are performed at a smaller spatial scale and therefore, they nicely complement the MVPA on large (entire cortex and lobes) and intermediate (ROIs) spatial scales.

2.3 Connecting the brain

As discussed in chapter 1, there are two theories about the etiology of DD. In chapter 6, we investigated by MVPA fMRI if the neural (symbolic and/or non-symbolic) number representations in the parietal cortex are impaired in adults with dyscalculia. In chapter 7, we tested if the connectivity towards these number representations are altered in adults with dyscalculia. Therefore, we have applied two different neuroimaging techniques to reveal both functional as structural connectivity. In the remainder of this section, I will explain these techniques.

2.3.1 fcMRI

Functional connectivity is defined as the temporal correlation between spatially defined brain regions. For each ROI of a subject you have a time series (averaged across all the voxels of that ROI) estimated with the univariate analysis. FcMRI simply correlates the time series of that ROI with the time series of another ROI. That way, functional connectivity is a misnomer, as we do not directly access the connectivity between two brain regions, but rather the correlation of the time series and therefore we cannot say anything about the direction or the causation of the connectivity between those two ROIs.

Before measuring fcMRI, the fMRI time series are additionally preprocessed to minimize the contribution of noise and artifacts. These additional preprocessing steps include: (1) bandpass filtering between 0.01 and 0.2 Hz (Balsters et al., 2016; Baria et al., 2013), (2) regression of head motion parameters and their first derivatives (3) regression of white matter and ventricle signals and their first derivatives (Ebisch et

al., 2013), (4) regression of task-related BOLD fluctuations (task = the contrast 'task minus baseline') (Boets et al., 2013; Ebisch et al., 2013), (5) scrubbing of motion-affected functional volumes (Power et al., 2012), and (6) spatial smoothing at 4 mm FWHM.

We applied this analysis in chapter 7 to compare functional connectivity between adults with and adults without dyscalculia.

2.3.2 Diffusion-weighted imaging

DWI is a variant of conventional MRI based on the tissue water diffusion rate (Le Bihan & Breton, 1985; Le Bihan et al., 1986; Merboldt et al., 1985; Taylor & Bushell, 1985). This imaging technique is based on the principle that diffusion of water molecules within white matter fibers of the brain is anisotropic, whereas diffusion of these molecules in cerebrospinal fluid and grey matter is isotropic (D. K. Jones & Leemans, 2011; Le Bihan & van Zijl, 2002).

The introduction of the diffusion tensor model enabled the indirect measurement of the degree of anisotropy and structural orientation that characterizes fibers (Basser et al., 1994). While DWI refers to the contrast of the acquired images, Diffusion Tensor Imaging (DTI) is a specific type of modeling of the DWI datasets. The basic concept behind DTI is that water molecules diffuse differently along the tissues depending their type, integrity, architecture, and presence of barriers, giving information about their orientation and quantitative anisotropy (Soares et al., 2013). With DTI analysis it is possible to infer, in each voxel, properties such as the molecular diffusion rate (Mean Diffusivity (MD)), the directional preference of diffusion (Fractional Anisotropy (FA)), the diffusion rate along the main axis of diffusion (Axial Diffusivity (AD)), and therate of diffusion in the transverse direction diffusivity (Radial Diffusivity (RD)). Diffusion in white matter is more restricted along the axon and tends to be anisotropic (directionally-dependent) whereas in grey matter is usually less anisotropic and in the CSF is unrestricted in all directions (isotropic) (Hagmann et al.,

2006). Based on this assumption, Basser et al. (1994) modeled the diffusion process by an ellipsoid, which can mathematically be represented by a 3×3 symmetric matrix, also known as tensor (hence DTI's name origin).

We applied DTI in chapter 7 as a measure of structural connectivity differences between adults with dyscalculia and their strictly matched controls.

3 The advantage of using multiple spatial scales with MVPA to uncover underlying representations

The contributions of the first author are:

- Literature study
- Co-development of simulation code
- Development of the code for the classification algorithms of empirical data
- Development of searchlight code for empirical data
- Collecting empirical data
- Perform all analyses
- Co-interpretation of simulation and empirical results
- Co-formulation of conclusions
- Text redacting

Published as

Bulthé, J., van den Hurk*, J., Daniels, N., De Smedt, B., & Op de Beeck, H.P. (2014). A validation of a multi-spatial scale method for multivariate pattern analysis. In 2014 International Workshop on Pattern Recognition in Neuroimaging (pp. 1-4). IEEE.*

Abstract

Most fMRI studies using MVPA restrict these analyses to merely one spatial scale. However, recently Bulthé, De Smedt & Op de Beeck (2014) used a multi-spatial scale method combining three levels of MVPA analysis on fMRI data from 16 subjects who performed a number comparison task: whole-brain MVPA, Regions Of Interest (ROI) based MVPA, and a small radius searchlight. The results of Bulthé, De Smedt & Op de Beeck (2014) clearly demonstrated the necessity of incorporating different spatial scales in MVPA analysis to draw conclusions on how the neural representations of the effects are distributed across the brain. We tested the validity of the method used in this empirical study by using three simulated fMRI datasets. Both simulated data and the real data (Bulthé, De Smedt & Op de Beeck, 2014) confirmed the relevance of analyzing data with MVPA on different spatial scales.

3.1 Introduction

MVPA has obtained a central role in the analyses of functional neuroimaging. MVPA focusses on the analysis and comparison of distributed patterns of activity. Detecting the patterns of activation makes MVPA a more sensitive method than univariate measures which average the fMRI signal in a certain Regions Of Interest (ROI) and compares the differences between conditions in their activity and thereby ignores the patterns underlying the activation. Different types of MVPA were developed and used to analyze distinct properties of fMRI data (Poldrack et al., 2011). First, a whole-brain MVPA is used to detect patterns of active voxels for a certain cognitive function regardless of the location in the brain. Second, ROI based MVPA methods have been used to detect patterns of active voxels within predefined regions. Third, searchlight MVPA (Kriegeskorte et al., 2006) includes a directive search through the entire scanned volume for specific information without restricting the region of the search. Searchlight uses a sphere around a center voxel to detect small regions with consist-

ent information content.

Most papers use only one of these levels of MVPA, or apply a searchlight analysis with a large radius and this sometimes even on a reduced set of the scanned volume (Eger et al., 2009; Schapiro et al., 2012; Christophel & Haynes, 2014; Walther et al., 2009). In this paper, we will describe the benefits of combining all three scales. We will demonstrate a number of simulation datasets which include different types of information, and apply each of the three levels of MVPA on the simulated datasets: small spatial scale (searchlight MVPA, cluster size of 33 voxels), intermediate spatial scale (ROI-based analysis), and large spatial scale (whole-brain MVPA). In the end, the combination of these three levels will provide more details on how centralized and/or distributed the information actually is. For example, if only the whole-brain MVPA shows significant decoding and the two other spatial scales are not significant, than the information in the scanned volume is very distributed across the scanned volume. Alternatively, if only the searchlight analyses show a significant result, than the information will be very focused at a certain location in the brain which is not well captured by pre-defined regions of interest. Additionally, we will link the results to the paper of Bulthé, De Smedt & Op de Beeck (2014) and show that the application of MVPA on different spatial scales helps to better understand fMRI data.

3.2 Materials & Methods

3.2.1 Data Simulation

Data simulations and computations were performed using custom Matlab R2012B code (Mathworks Inc, Natick, MA), combined with the LIBSVM algorithm (`http://www.csie.ntu.edu.tw/~cjlin/libsvm/`). We created three different voxel patterns: a small center cluster (from here on referred to as Central), 4 small clusters (Decentral) and a fully distributed pattern (Distributed)(Figure 3.1). The patterns were centered in a [20 * 20 * 10] volume resulting in 4000 voxels (size similar to the grey matter of a cortical lobe), and all consisted of 2 classes of voxels, labeled voxA and

voxB, to simulate voxels that respond differently to 2 conditions. In condition 1, all voxA voxels yielded an activity of 1, and all voxB voxels an activity of -1. Condition 2 elicited opposite patterns, with voxA yielding an activity of -1 and voxB an activity of 1.

The volumes were copied 10 times for condition 1, and 10 times for condition 2 as to simulate runs, or trials. For each trial, a response variability across trials was simulated by adding or subtracting a random effect variability value ($\pm$ 1) for each pattern voxel, while preserving the average response per voxel across trials. The patterns were subsequently smoothed (because real data is correlated while noise is uncorrelated) by convolving them with a 3D Gaussian kernel (full-width at half maximum (FWHM) = 2 voxels). A white noise volume was created and smoothed with an identical kernel. The desired signal-to-noiseratio (0.04) was obtained by multiplying the noise volume by a predefined scalar before adding the noise to the pattern volume.

Table 3.1: The number of informative voxels included in the three types of ROI for every simulated dataset

Number of voxels included	Total number of informative voxels	ROI's		
		ROIc	ROIi	ROIp
Central	72	6	34	72
Clustered	104	8	48	104
Distributed	1600	100	250	1600

3.2.2 ROI selection for simulated and empirical data

For each simulated dataset three types of ROIs are defined (Table 3.1). Each ROI has a total of 250 voxels included, however, the number of informative voxels differs for each type of ROI. The first kind of ROI (ROIc) includes the number of informative voxels at chance level. For example, if the total simulated volume includes 4000 voxels with a ROI of 400 voxels and there are 40 informative voxels, the ROI with a number of informative voxels at chance level will include 4 informative voxels. The

second type of ROI (ROIp) compromises all the informative voxels and is in that sense a perfect ROI, e.g. the 40 informative voxels will all be included in the 400 voxels of the ROI. Thirdly, an intermediate ROI (ROIi) is created between those two extremely defined ROI, encompassing 18 (N informative voxels - N informative voxels at chance level) informative voxels. A remark has to be made concerning the number of voxels included in the perfect ROI for the distributed scenario, this ROI has 1600 voxels included so that the perfect ROI has all the informative voxels.

The ROIs of the real empirical dataset were selected with independent data that was not used in the SVM analyses. The IPS was theoretically chosen because it has been reported to be involved in numerical processing (Dehaene et al., 2003), (Piazza et al., 2007). The whole brain activation contained all the voxels that resulted from the localizer scans on subject level.

3.2.3 Pattern Classification

Concerning the pattern classification for both simulated and empirical data, the decoding pattern classification analysis were implemented by applying linear SVMs using the LIBSVM Matlab toolbox with the default parameters. We opted for the default values of parameters such as optimal c, because many previous MVPA fMRI papers also have used these default values (e.g. Zorzi et al. (2011); Raizada et al. (2010); Bulthé, De Smedt & Op de Beeck (2014)). In this way the MVPA approach described here is applicable for many MVPA fMRI papers.

During the training of the linear SVM 70% of the data was used to construct the hyperplane that best separated the data of the two conditions. The performance of the classifier on this pairwise classification was calculated for the average data of the remaining 30% of the runs (repeated 100 times (empirical data) or 50 times (for simulated data, to decrease computation time) per pair of conditions with a random assignment of runs to the training and test sets).

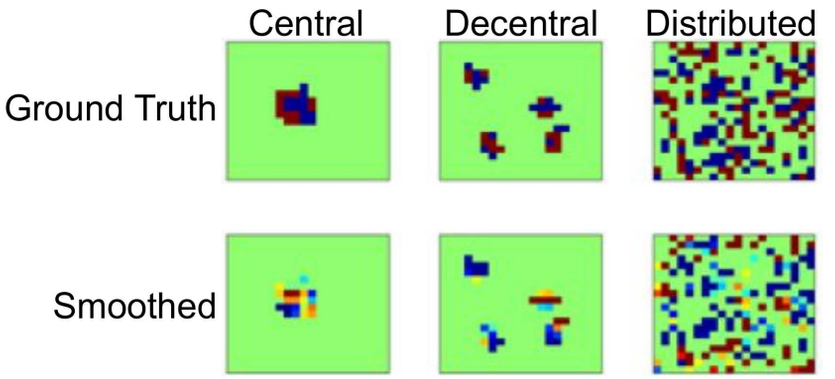

Figure 3.1: The ground truth and its smoothed maps of the three simulated datasets.

3.3 Results

3.3.1 Experiments on the simulated data

Central located information The results of the centralized informative voxels are shown on the first row of Figure 3.2. The whole-brain analysis has an accuracy of 56% (95% CI = [47-80%]). Note that in this total volume of 4000 voxels, only 72 voxels are informative for classifying the two conditions. The accuracy in the ROIp, including all the informative voxels is 78% (95% CI = [58-96%]). The more realistic intermediate ROIi has a classification of 68% (95% CI = [53-85%]), which is much higher than the ROIc including a chance-level proportion of informative voxels (52%) (95% CI = [47-76%]). The whole-brain and ROI-based analysis are not able to localize the informative voxels because only 72 voxels are informative in the simulated data, while in the whole-brain analysis all 4000 voxels seem to be informative and in the ROI analysis 250 voxels are considered informative. In this case, the searchlight analysis seems to do the best job. The searchlight analysis gives high accuracies for the informative voxels in this scenario and the localization fits well with the ground truth. In sum, when the information is located in a small local patch and there are not too many informative voxels, a searchlight method is the best approach.

Decentral located information The whole-brain analysis, on data which has the information more spread across the volume in clusters, has an accuracy of 56% (95% CI = [45-78%]) (second row of Figure 3.2). This accuracy is just slightly better than

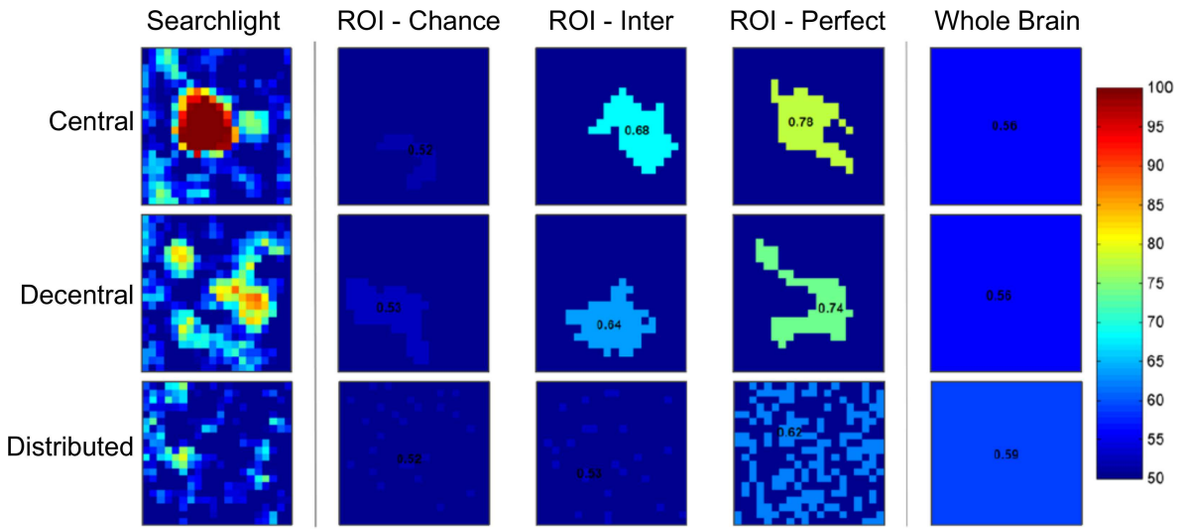

Figure 3.2: Overview of the accuracies for each of the three levels of MVPA (searchlight, three types of ROI, and whole-brain analysis) per type of information (central, clustered, and distributed located).

the accuracy of ROIc (53%) (95% CI = [48-78%]). The ROI between chance level and perfect level ROIi has an accuracy of 64% (95% CI = [54-92%]), demonstrating a successful classification between both classes. The perfect ROIp including all informative voxels gives a performance of 74% (95% CI = [56-94%]). In contrast to the central located information scenario, the searchlight analysis does not locate the majority of the informative voxels in the scanned volume. One cluster on the bottom left of the volume is poorly localized and the two other clusters on the right are merged together. In this decentral clustered scenario, the ROI-based analysis seems to be the preferable approach opposed to the searchlight and the wholebrain analysis, provided that the a priori defined ROI includes a high proportion of informative voxels.

Distributed located information In the distributed scenario, the same information is present as in the other scenarios with the exception that this information is distributed across 1600 voxels in the volume. The ROIc at chance level and the in-between ROIi do not give a succesful classification of both classes (52% (95% CI = [46-75%]) and 53% (95% CI = [47-76%]), respectively) (third row in Figure 3.2). Again, ROIp gives a good accuracy of 62% (95% CI = [53-85%]). However, it is not realistic to assume that one would have such a perfect ROIp in real data. The searchlight result

does not seem to give any clear-cut informative voxels at all. Based on the results of the searchlight and the more realistic ROIi, one would assume that there is no classification possible between the two classes. On the contrary, the whole-brain MVPA with an accuracy of 59% (95% CI = [52-88%]) shows that there are informative voxels present. All things considered, in this case the whole-brain approach seems to be the best method to test whether there is any classification possible between the two classes. Combined with the failure of the two other approaches, it shows that the information is distributed across many voxels.

3.3.2 Experiments on real data: a number comparison task

Input data Here we summarize the properties of the empirical data, more information can be found in Bulthé, De Smedt & Op de Beeck (2014). Sixteen healthy subjects performed a number comparison task with symbolic and non-symbolic numbers while fMRI data were acquired with a 3T Philips Intera Scanner (48 slices, slice thickness 2mm, interslice gap 1mm, TR = 3000 ms, TE = 30 ms, flip angle = 90 degrees, 104 $\times$ 104 matrix). A short-block design was used with variable block duration (4-6 seconds). Eight conditions were included, namely four numerosities (2, 4, 6 and 8) and two formats (non-symbolic numbers (dots) and symbolic numbers (digits)). Each condition was repeated six times in each run and at least 12 runs were presented for each subject. The contrast of interest was the number comparison task $>$ fixation. The data were realigned, spatially normalized and smoothed using Gaussian kernels of 4 mm full-width at half maximum. Subsequent analysis showed no differences between smoothed data and unsmoothed data, which corresponds to Op de Beeck (2010).

Activation of non-symbolic numbers The whole-brain classification accuracy was 85% ($t[15] = 11.66$, $p < 0.001$). A t-test was chosen as statistic to be in line with previous MVPA fMRI papers about numerical cognition (Damarla & Just, 2012)-(Eger et al., 2009). The ROI-analysis of the IPS resulted in a classification accuracy of 74% ($t[15] = 7.36$, $p < 0.001$) (Figure 3.3), and many other ROIs also revealed high

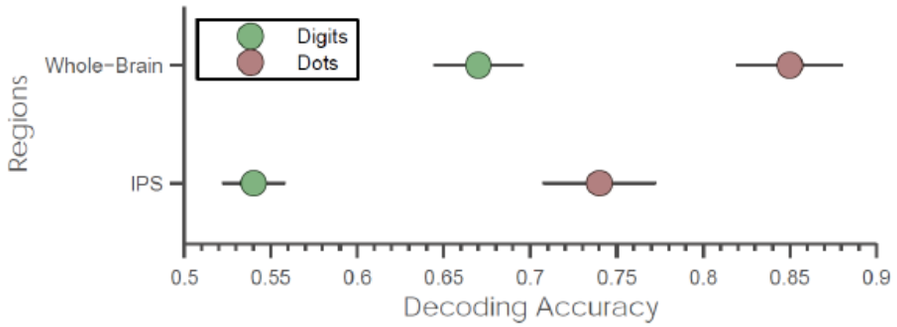

Figure 3.3: Whole-brain and ROI accuracy and standard bar of error for both digits and dots in the real dataset.

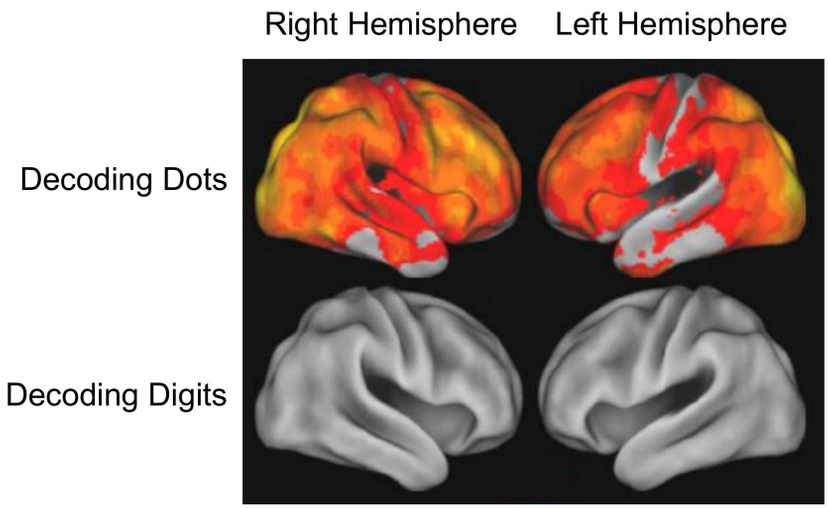

Figure 3.4: Results of the whole-brain searchlight analysis for the real data set for FDR-corrected threshold of $t = 2.5$.

decoding accuracy (see Bulthé, De Smedt & Op de Beeck (2014) previous paper). The outcome of the searchlight analysis with a 2-voxel radius shows clear decoding in many regions (Figure 3.4), together with the ROI and whole-brain analysis, that non-symbolic numbers are present on a local, intermediate and large spatial scale.

Activation of symbolic numbers The results of the digits were very different from the non-symbolic numbers. First of all, the searchlight result showed no informative voxels in the entire scanned volume (Fig. 4). Secondly, the ROI classification accuracy was not very high in comparison to the non-symbolic numbers accuracy (54% and 74%, respectively), although the classification of digits was significant in the IPS ($t[15] = 2.31, p = 0.02$) (Fig. 3). Thirdly, the most promising result was the outcome of the whole-brain analysis: 67% correct classification ($t[15]$ 6.74, $p < 0.001$). These

three results combined, suggest that information representing symbolic numbers is distributed across many voxels across the scanned volume and that many the voxels combined are necessary to get a good classification accuracy.

3.4 Discussion

In this paper we presented a multi-spatial scale MVPA method to test how informative voxels are located in a scanned fMRI volume.

The results of the analysis on the simulated data revealed that each type of MVPA has its own strength in localizing informative voxels in a scanned volume. The searchlight MVPA has the best accuracy when the information is very strong and local. The ROI analysis detected the highest number of informative voxels when these voxels are scattered but still clustered within the scope of the ROI. Finally, the whole-brain analysis outperformed both the ROI and searchlight analysis in the case that the information was even more scattered across the entire scanned volume.

The real fMRI dataset was analyzed using the same three types of MVPA and yielded equivalent results. If the analysis of the data for the digits would have been restricted to ROI and searchlight analysis, than the results would have suggested that hardly no information is present for this class. However, implementing the whole-brain MVPA clearly shows that different digits can be distinguished from each other. Clearly, the informative voxels which needed to be detected were scattered across the scanned volume. The same was the true for non-symbolic numbers, but in that case the different numerosities were very easy to distinguish so that information was present at each of the three spatial scales: small (searchlight), intermediate (ROI), and large (whole-brain MVPA) spatial scale.

Considering real fMRI data, an remark is that one can often not know how well the ROI is defined. This can be checked by defining an outside-ROI including all the voxels which are not inside the real ROI. The MVPA accuracy can be compared

between the outside-ROI and the real ROI, provided that ROI size (number of voxels) is matched. The real ROI is helpful if the accuracy of the real ROI analysis is higher than the accuracy of the outside-ROI analysis.

A final remark concerns the comparison from the ROI-based classification and the whole-brain classification with the searchlight results. Searchlight is a method for localizing local relevant information. Thus a comparison of accuracies across the three methods would be possible only if maps from the searchlight were thresholded and used as features for further classification analysis. However, this approach would require optimization of the threshold value, what would be computationally expensive and in this context not feasible.

3.5 Conclusion

This paper suggests that it does not suffice to run just a single MVPA method or a searchlight analysis with a large radius. Rather, one has to detect how information is distributed across different spatial scales by using a combination of wholebrain, ROI, and searchlight analysis. Moreover, the analysis of the real fMRI dataset revealed that useful information can be overlooked when one does not use such a combination of spatial scales.

Acknowledgments

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Part II

Relationship between symbolic and non-symbolic number representations

4 Symbolic and non-symbolic representations are processed differently in the human cortex

The contributions of the first author are:

- Literature study
- Development of the code for the classification algorithms of empirical data
- Development of searchlight code for empirical data
- Collecting empirical data
- Perform all analyses
- Co-interpretation of empirical results
- Co-formulation of conclusions
- Text redacting

Published as

Bulthé, J., De Smedt, B., & Op de Beeck, H.P. (2014). Format-dependent representations of symbolic and non-symbolic numbers in the human cortex as revealed by multi-voxel pattern analyses. NeuroImage, 87, 311-322.

Abstract

Neuroimaging studies in the last 20 years have tried to unravel the neural correlates of the number processing across formats in humans and non-human primates. Results point to the intraparietal sulcus as the core area for an abstract representation of numerical quantity. On the other hand, there exists a variety of behavioral and neuroimaging data that are difficult to reconcile with the existence of such an abstract representation. In this study; we addressed this issue by applying MVPA to fMRI data to unravel the neural representations of symbolic (digits) and non-symbolic (dots) numbers and their possible overlap on three different spatial scales (entire lobules, smaller regions of interest and a searchlight analysis with 2-voxel radius). Results showed that numbers in both formats are decodable in occipital, frontal, temporal and parietal regions. However, there were no overlapping representations between dots and digits on any of the spatial scales. These data suggest that the human brain does not contain an abstract representation of numerical magnitude.

4.1 Introduction

The neural mechanisms of numerical cognition have been intensively investigated in behavioral and neuroimaging research (for review see Ansari (2008); Nieder & Dehaene (2009)) due to the central role of numbers in daily life and education (Gerardi et al., 2013; Lipkus & Peters, 2009; Nelson et al., 2008; Reyna et al., 2009). A core theme in this research deals with the question of representational overlap between symbolic (e.g. Arabic digits) and non-symbolic (e.g. arrays of dots) magnitudes. This issue has been approached by comparing the brain activity during non-symbolic as well as symbolic tasks and by searching for regions that are commonly active while processing these two formats of numerical magnitudes. Both approaches have provided evidence in favor of the existence of an abstract representation of numerical magnitudes and the accumulating evidence suggests that the intraparietal

sulcus (IPS) hosts a core module for processing numerical magnitude (Dehaene & Cohen, 1997; Eger et al., 2003; Pinel et al., 2001a).

More recently, it has been suggested that the MVPA of fMRI data might be an interesting method to probe the abovementioned question. This method provides a more fine-grained understanding of the nature of the activated numerical representations (Raizada et al., 2010). The existing body of data that has been interpreted in favor of an abstract representation of numerical magnitude is typically based on null results, indicating no differences between symbolic and non-symbolic formats in behavioral tasks and in activity in the IPS. Such null results are, however, difficult to interpret, as they can occur due to insufficient power to detect a difference. The present study attempts to overcome this issue by applying MVPA of fMRI data on ROIs throughout the entire cortex (a) to test if symbolic and non-symbolic numerical magnitudes are processed in the same brain areas, and (b) to investigate the amount of representational overlap between both formats in those brain areas. Although MVPA analyses have been applied to investigate numerical processing (Damarla & Just, 2012; Eger et al., 2009; Raizada et al., 2010), the present study extends the existing body of evidence in two important ways. First, this study is the first to apply MVPA not only in the IPS but also outside the parietal cortex. This allowed us to test the existence of a format-independent system for representing numerical magnitudes. Second, we also used MVPA searchlight analysis in the whole cortex to uncover other possible (common) areas for processing symbolic and non-symbolic magnitudes.

There has been a longstanding behavioral tradition in attempting to reveal the common representation of different numerical formats (Barth et al., 2003; Buckley & Gillman, 1974; Dehaene & Akhavein, 1995; Jaffe-Katz et al., 1989; Naccache & Dehaene, 2001; Shepard et al., 1975). One of the most important findings is the so-called numerical distance effect (Moyer & Landauer, 1967). The numerical distance effect is the observation that reaction times increase and accuracy rates decreases in number comparison tasks when numerical magnitudes are closer in distance than when they are further apart. This effect has been observed in children (Feigenson et al., 2004;

Lonnemann et al., 2011; Holloway & Ansari, 2010; Sekuler & Mierkiewicz, 1977), adults (Dehaene et al., 1990; Dehaene, 1992; Moyer & Bayer, 1976) and animals (Brannon et al., 2001; Nieder & Miller, 2003) and it has been contended that this indicates a similar way of representing numerical magnitudes across different species and ages. Moreover, this numerical distance effect seems to be similar for symbolic and non-symbolic stimuli, which suggests a common numerical magnitude system for different formats (Dehaene et al., 1990).

Neuroimaging studies in the last 20 years have tried to unravel the neural correlates of this numerical distance effect and number processing across formats in humans and non-human primates. Results have pointed to the IPS as the core area for the representation of numerical magnitude because of three main findings: (a) the IPS is involved in magnitude processing in humans (for a meta-analysis and review see Ansari (2008); Nieder & Dehaene (2009)) and primates (Nieder et al., 2002; Nieder & Miller, 2003; Sawamura et al., 2002); (b) the IPS activity correlates with the distance between numerical magnitudes in humans (Ansari, Dhital & Siong, 2006; Cohen Kadosh et al., 2005; Piazza et al., 2007; Pinel et al., 2004); (c) the IPS activity does not differ between formats in humans (Eger et al., 2003; Fias et al., 2003; Piazza et al., 2007).

Although these findings have been replicated with different paradigms and tasks, the abstract processing of numerical magnitudes and the function of the IPS as number module remain a debated issue. More specifically, some behavioral and neuroimaging observations are very difficult to reconcile with the abstract view on magnitude processing (for extensive discussion, see Cohen Kadosh & Walsh (2009a)). For example, Gebuis & Reynvoet (2012a) have shown that the processing of non-symbolic magnitude is more grounded in low-level visual parameters than the processing of symbolic quantities. Lyons et al. (2012) found that comparing numerical magnitudes across formats is more difficult than comparisons within one format, suggesting that additional processing is required for cross-format comparisons. The experiments of Maloney et al. (2010) demonstrated that the distance effect of non-symbolic mag-

nitudes is not correlated with that of symbolic magnitudes. Furthermore, children with developmental dyscalculia are more impaired in symbolic tasks compared to non-symbolic tasks (De Smedt & Gilmore, 2011; Iuculano et al., 2008; Landerl & Kölle, 2009; Rousselle & Noël, 2007). Finally, a recent review by De Smedt et al. (2013) on the association between numerical magnitude processing and individual differences in mathematics achievement indicated that in typically developing children, measures of symbolic but not non-symbolic number processing are reliable predictors of individual differences in mathematics achievement (De Smedt et al., n.d.). In sum, these behavioral data are difficult to reconcile with an abstract representation of numerical magnitudes.

This abstract representation of numerical magnitudes has also been challenged by patient and neuroimaging studies. A study on patients with damage to the left supramarginal gyrus showed a dissociation between the processing of symbolic and non-symbolic magnitudes (Polk et al., 2001). Neuroimaging studies have demonstrated that the IPS contains an abstract representation of numerical order rather than numerical magnitude (Fias et al., 2007; Ischebeck et al., 2008) and that activity in the IPS while performing a numerical task was related to response-selection rather than numerical processing per se (Cappelletti et al., 2010; Göbel et al., 2004).

Whether or not numerical magnitudes are processed in an abstract way in the IPS has been subject to a continuing discussion in the numerical cognition domain (Cohen Kadosh & Walsh, 2009b). One of the main issues in this debate is the fact that evidence for an abstract representation of numerical magnitudes is based on null results, indicating no differences across formats in activation in the IPS. It is crucial to point out that these null results emerge from fMRI studies that have used univariate methods to measure the overall regional activity for different conditions. Such data, however, limit our understanding of the information encoded by neural populations in that region. Recently, it has been suggested that the application of MVPA to fMRI might be one way to solve this issue (Ansari, 2008; Cohen Kadosh & Walsh, 2009b; Dehaene, 2009).

MVPA allows to identify spatial patterns of brain activity of different stimuli in a certain region of interest (Norman et al., 2006). Two previous studies have used MVPA to relate the processing of symbolic and non-symbolic formats directly to each other. Damarla & Just (2012) showed that the neural codes for quantities of objects, e.g., a picture of three tomatoes or the digit 3 with a picture of one tomato, can be accurately decoded in the parietal cortex. Eger et al. (2009) compared the activation patterns evoked by dot patterns and digits (numbers 2, 4, 6 and 8) in the parietal cortex. The activation patterns non-symbolic and symbolic magnitudes were distinguishable at the individual level and they could be significantly decoded in the parietal cortex. However, the decoding was less accurate for symbolic compared to non-symbolic magnitudes. Eger et al. (2009) also applied cross-format generalization, showing significant generalization from symbolic to non-symbolic magnitudes but not from non-symbolic to symbolic. The studies of Damarla & Just (2012) and Eger et al. (2009) demonstrated that MVPA has the sensitivity that is required to investigate the representations of magnitudes. These data also suggested at least some communality in symbolic and non-symbolic representations of magnitudes.

Similar to the study of Eger et al. (2009) we investigated the representation of numerical magnitude in the context of a comparison task. However, we extended their design in three important ways. First, given the growing literature, which shows that non-symbolic comparison tasks involve a lot of non-numerical processes (Gilmore et al., 2013; Gebuis & Reynvoet, 2012b,a), we implemented a whole-brain approach to define the relative importance of the different lobules. Our approach consisted of including a large set of ROIs and searchlight analysis. In these analyses we targeted the neural representations of number at multiple spatial scales: a large spatial scale (the entire cortex, frontal, parietal, occipital and temporal lobes), an intermediate spatial scale (ROIs in the four cortices) and small scale (a whole-brain searchlight analysis with a radius of twice the voxel size). Second, Eger et al. (2009) only used ten subjects, but we aimed to replicate this in a larger sample of 16 subjects. Third, the paradigm of Eger et al. (2009) was an event-related fMRI design in which each

trial involved the presentation of a sample number followed by a match number. Participants had to indicate whether the match number was smaller or larger than the sample number. We opted for a fixed comparison task in which each of the numbers (2, 4, 6 and 8) had to be compared to the fixed reference number 5 and control in this way for possible context-dependent effects on the number representations. The consequence of this fixed comparison task, is that different from Eger et al. (2009) we cannot look into the neural representations of numerical magnitudes without the context of a comparison task.

We expected accurate decoding performance for both symbolic and non-symbolic magnitudes. If this decoding would be limited to the IPS, this would favor the existence of a format-independent module for representing numerical magnitudes. On the other hand, if decoding performance would be observed across various brain areas, this would suggest that the representation of magnitudes would be more widely distributed throughout the brain. We also predicted that a neural distance effect would occur for both formats in the regions with accurate decoding. The decoding performance for small distances should be lower than for large distances. Finally, we tested the generalization between the two numerical formats. Such generalization should occur if there is an abstract representation of number. However, the absence of generalization between the two formats would indicate that there is no such abstract representation of numerical magnitude.

4.2 Materials & Methods

Participants

Sixteen healthy subjects participated in the fMRI study (four males, aged between 21-28 years, two left-handed) and were paid for participation. All participants had normal or corrected-to-normal vision and reported no neurological or psychiatric history. No effects of handedness or sex were observed. The study was approved by the medical ethics committee of the KU Leuven. All participants provided informed

consent prior to scanning.

Stimuli

Images (400 x 400 pixels) consisted of centered white circles on a black background. Within the white circles either dots or Arabic digits were displayed comprising 2, 4, 6 or 8 as numerosities. Dot displays were controlled for possible confounding parameters, such as intensive parameters (individual item size and inter-item spacing) and extensive parameters (total luminance and total area spanned by the dots). This was done by using the method and automated program created by Dehaene et al. (2005), similar to many other fMRI-studies that used dot patterns as their stimuli (Eger et al., 2009; Roggeman et al., 2011; Santens et al., 2010). Both intensive and extensive parameters were randomly varied across the dot displays by an adapted version of a Matlab program (Matlab 7.13.0, The MathWorks, Inc., Natick, MA) described in Dehaene et al. (2005). To avoid adaptation for the symbolic numbers, the symbols varied in position and size across trials.

Apparatus

The fMRI data were acquired in a 3T Philips Intera Scanner (Department of Radiology of KU Leuven) with a 12-channel head coil and with an EPI sequence (48 slices, 2.1 x 2.1 mm inplane voxel size, slice thickness 2 mm, interslice gap 1 mm, TR = 3000 ms, TE = 30 ms, flip angle = 90, 104 x 104 matrix). Accurate timing of the stimuli relative to fMRI acquisition was achieved with an electronic trigger at the beginning of each run. For each participant, a high-resolution T1-weighted anatomical image was obtained (182 slices, resolution 0.98 x 0.98 x 1.2 mm, TR = 9.6 ms, TE = 4.6 ms, 256 x 256 acquisition matrix).

Stimulus presentation in all tasks was controlled via Psychtoolbox 3 (Brainard, 1997). We used a Barco 6400i LCD projector (resolution 1024 x 768, refresh rate 75 Hz) to project the stimuli on a vertical screen. The stimuli were positioned approximately 35 cm from participants' eyes, and were visible via a mirror attached to the head-coil.

Design

The design of the experimental runs is illustrated in Figure 4.1. We used a short-block design with variable block duration, i.e. one block comprised either 4, 5 or 6 seconds. Each run consisted of 48 experimental blocks (each condition was presented in 6 blocks) and 7 fixation blocks (baseline). Two fixation blocks were presented for 8 seconds at the beginning and at the end of the run, the remaining five fixation blocks lasted 4, 5 or 6 seconds and were presented after each 8th experimental block. During each experimental block, one particular number was repeated in the same format in sequences of 4, 5 or 6 trials. Each trial was presented for 1000 ms, during which a random exemplar of the number was shown for 200 ms and followed by a fixation cross for 800 ms. In total, one run lasted 280 seconds and 12-14 runs were presented to participants (Figure 4.1).

Participants had to perform a number comparison task in the experimental runs. We selected this task because it allowed us to explicitly access the numerical magnitude representations (Piazza et al., 2004a; Pinel et al., 2004; Zorzi et al., 2011). Participants were instructed to evaluate whether the presented number was smaller or larger than five whenever the displayed format or numerosity changed.

In two localizer runs, we used a subtraction task. In this task participants had to subtract two numbers ranging from 1 to 20 and they had to indicate whether the solution was odd or even. In each trial the subtraction problem was presented for 1700 ms and followed by a fixation cross for 300 ms.

Analysis

fMRI preprocessing

The data were processed with the Statistical Parametric Mapping software package (SPM8, Welcome Department of Cognitive Neurology, London), as well as custom Matlab code. Anatomical images were normalized to the standard brain template

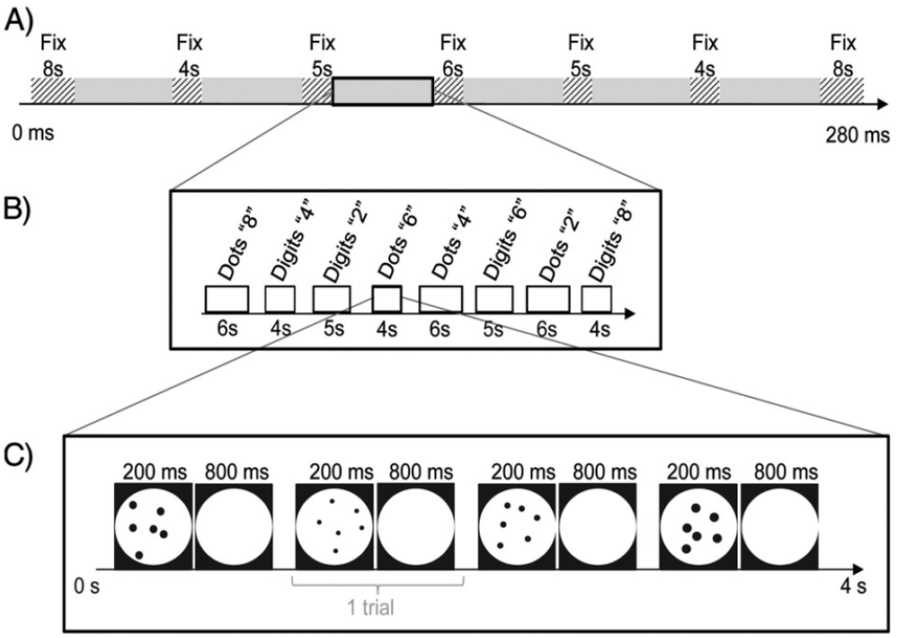

Figure 4.1: Overview of the experimental design; a. One run lasted 280 seconds and consisted of 7 fixation blocks between the experimental blocks; b. Example of 8 experimental blocks; c. Example of one experimental block comprising 4 trials.

defined by the Montreal Neurological 152-brains average. Functional images were corrected for slice-timing differences and realigned to the first image to correct for head movements. Spatial normalization was done using the parameters obtained in the normalization of the anatomical images. During normalization functional images were re-sampled to a voxel-size of $2 \times 2 \times 2$ mm. Finally functional images were spatially smoothed using Gaussian kernels of 4 mm FWHM. It could be that spatial smoothing affects the decoding analyses, although Op de Beeck et al. (2010) observed that smoothing does not decrease the sensitivity of decoding analyses. Against this background, we tested whether there was a significant difference between the decoding accuracy of smoothed and unsmoothed data. These data revealed no significant differences between the regions of interest (decoding symbols: $F_{(1,22)} = 0.513$, $p = 0.48$ and decoding dots: $F_{(1,22)} = 0.028$, $p = 0.87$), which corresponds to Op de Beeck et al. (2010).

Statistical analysis

The experimental effects in each voxel were estimated by a multi-session design matrix that modeled the data at the block level. A general linear model was created with regressors for each participant for each condition. The six motion realignment parameters were additionally included as regressors to account for signal variations due to head movements. Subsequent analyses were performed using t-statistics (resulting from the contrast of each condition versus baseline) per run that were obtained after fitting the general linear model.

Regions of Interest

Twenty-three ROIs were defined on a subject level using the functional data from the localizer scans (contrast of task minus fixation) and the anatomical WFU PickAtlas Toolbox (Wake Forrest University PickAtlas, `http://fmri.wfubmc.edu/cms/software`) when the ROI was available in the toolbox (Maldjian et al., 2003). The selection of ROIs was theoretically guided by including ROIs that have been reported to involved in numerical processing (Dehaene et al., 2003; Holloway et al., 2013; Lyons & Ansari, 2009; Maruyama et al., 2012; Piazza et al., 2007; Santens et al., 2010; Zago et al., 2001; Zhang et al., 2012).

We selected the ROIs on different spatial scales: (a) large spatial scale (the entire cortex, frontal, parietal, temporal, occipital cortex, frontal + parietal + temporal cortex and frontal + parietal cortex); (b) intermediate spatial scale (IPS, left and right superior parietal lobule, inferior occipital cortex, superior temporal sulcus, visual word form area, Wernicke's area, fusiform gyrus, left and right inferior frontal gyrus, and left and right superior frontal gyrus; (c) small spatial scale (left and right anterior IPS, and left and right posterior IPS). The contrast for defining the ROIs was thresholded at a minimum of $p < 0.001$ (uncorrected for the number of voxels). The 'All Regions' ROI contained all the voxels that resulted from the localizer runs in each subject.

Pattern classification

We implemented decoding and generalization pattern classification analysis for every ROI by applying linear SVM using the OSU SVM Matlab toolbox with the default parameters of this toolbox as described by Op de Beeck et al. (2010). We used a radial basis function kernel as decision function with the parameter gamma set to 1. The type of the classification algorithm was C-SVC with C set to 1. During the training of the linear SVM 70% of the data was used to construct the hyperplane that best separated the data of the two conditions. The performance of the classifier on this pair-wise classification was calculated for the average data of the remaining 30% of the runs (repeated 100 times per pair of conditions with a random assignment of runs to the training and test sets). For decoding pattern classification, the pair-wise classification was performed on the same condition pairs during training and testing. The higher the decoding accuracy, the better the classifier was able to discriminate between two conditions. For generalization pattern classification, different condition pairs were used to train versus test the performance of the classifier. A higher accuracy for the generalization analyses suggests an overlap in the neural representations for the training conditions and the test conditions. We also performed analyses with correlation-based MVPA instead of linear classifiers, which resulted in similar conclusions as the decoding accuracies.

Distance effect analysis

To test for a neural distance effect, we examined how the pairwise classification results varied with the numerical distance between the two classified numerical magnitudes. We applied a regression analysis in Matlab with the three possible distances (2, 4 and 6) as predictors and the decoding classification performance for that distance as the dependent variable for those ROIs that showed a significant decoding effect.

Searchlight analysis

The SLA is a MVPA method introduced as a technique for localizing functional regions that carry out a particular type of information. This method particularly suited for finding where in the brain the local spatial activity pattern differs across conditions (Kriegeskorte et al., 2006; Kriegeskorte & Bandettini, 2007). These analyses are performed at a smaller spatial scale and therefore, they nicely complement the MVPA on large (entire cortex and lobes) and intermediate (ROIs) spatial scales.

For the SLA a sphere with a radius of twice the voxel size (which includes 33 voxels, if all the surrounding voxels are within the brain volume) was sequentially moved across the entire volume (non-brain volumes areas were left out of the analysis). White matter was included in the resulting maps of decoding accuracy, generalization accuracy and neural distance effect for each subject. Afterwards the maps were spatially smoothed using Gaussian kernels of 6 mm FWHM. These output images of all subjects were submitted to a second-level random effects analysis with SPM8. In this analysis, the average accuracy of pattern classification tests for each voxel was compared to chance level (0.50) and the group t-map that contains the corresponding t-value for each voxel was generated (Lee et al., 2011; Raizada et al., 2010; Walther et al., 2009). To correct for multiple comparisons the false discovery rate was set at $p = 0.05$.

4.3 Results

4.3.1 Behavioral Results

A two-way repeated-measures (distance x format) ANOVA was performed on the accuracy and reaction times of the number comparison task for symbolic and non-symbolic magnitudes. For accuracy, there was significant main effect of distance ($F_{(1,15)} = 15.24$, $p = 0.001$) suggesting more accurate responses for larger distances than for smaller distances. There was no main effect of format ($F_{(1,15)} = 1.004$, $p =$

0.332) and no distance x format interaction ($F_{(1,15)} = 0.017$, $p = 0.897$).

Turning to the reaction times, we found a significant main effect of distance ($F_{(1,15)} = 90.629$, $p < 0.001$). Participants responded faster to larger distances than to smaller distances. There was also a significant main effect of format ($F_{(1,15)} = 83.457$, $p < 0.001$), with faster reaction times for symbolic magnitudes than for non-symbolic magnitudes, and a significant distance x format interaction ($F_{(1,15)} = 38.575$, $p < 0.001$) which indicated a larger distance effect for non-symbolic magnitudes compared to symbolic magnitudes.

To examine the association between the behavioral symbolic and non-symbolic distance effects, we calculated for each participants a linear regression in which the reaction times for each task was predicted by distance. R^2-squared values for each regression were used as indeces of the distance effect. No significant correlation between the distance effects for symbolic and non-symbolic magnitudes was observed ($r = 0.108$, $p = 0.69$).

4.3.2 fMRI Results

Localizer

Participants had an average accuracy of 85.93% (standard deviation (SD) = 6.26) on the subtraction task. A second-level analysis on the fMRI localizer data was applied to the contrast 'subtraction task minus fixation' for all the subjects. We observed significant activation in multiple regions across the entire cortex, including the IPS, inferior and superior frontal gyri, supramarginal and angular gyri, inferior occipital cortex and superior parietal cortex. Results are shown in Figure 4.2 and Table 4.1.

Symbolic and non-symbolic representations: large spatial scale (entire cortex and lobes)

We first investigated if symbolic and non-symbolic representations, distance effects for both formats and an the association between digits and dots can be detected on a

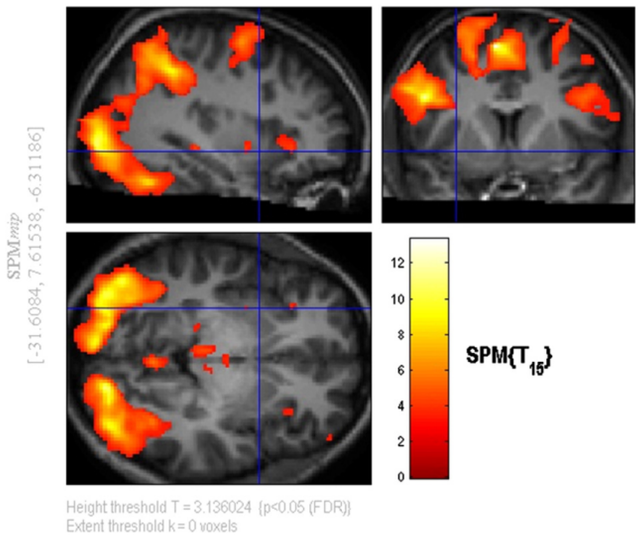

Figure 4.2: Statistical map of brain regions that were found to exhibit significantly higher levels of activations during the subtraction task compared to fixation (multiple comparisons corrected with FDR = 0.05, mapped onto an anatomical image of one of the participants).

ROI	x	y	z	$t[15]$	p
Left supramarginal angular	-8	8	60	13.32	< 0.001
Left precentral gyrus	-50	5	28	13.16	< 0.001
hIP3	-22	-55	40	11.76	< 0.001
Left inferior occipital cortex	-44	-86	-8	10.62	< 0.001
Right superior parietal cortex	24	-55	50	10.12	< 0.001
Left superior parietal cortex	-22	66	44	10.02	< 0.001
Right inferior occipital cortex	42	-84	-8	9.15	< 0.001
Right IPS	32	-52	46	8.83	< 0.001
Right fusiform gyrus	44	-76	-18	8.46	< 0.001
Left IPS	-44	-44	42	8.45	< 0.001
Left fusiform gyrus	-46	-62	-20	7.89	< 0.001
Right superior frontal gyrus	32	4	64	5.59	0.002
Right inferior frontal gyrus	48	10	28	5.23	0.003
Left insula	-26	24	2	5.01	0.003
Right middle frontal gyrus	44	0	54	4.97	0.004
Left superior frontal gyrus	-20	8	70	4.94	0.004
Left inferior frontal gyrus	-32	28	-4	4.2	0.011
Left middle frontal gyrus	-42	38	28	4.05	0.013
Right precentral gyrus	42	2	40	3.27	0.013

Table 4.1: List of regions activated by the localizer subtraction task. Multiple comparison correct with FDR = 0.05. The x, y, z coordinates are the MNI-coordinates of each activation peak. hIP3 is a cytoarchitectonic defined subregion of the IPS (Caspers et al., 2006).

large spatial scale.

Decoding accuracies For both non-symbolic and symbolic magnitudes the classifier was able to discriminate activation patterns of different magnitudes significantly better than chance level in the entire cortex, frontal cortex, parietal cortex, occipital cortex, frontal + parietal + temporal cortex, and frontal + parietal cortex (Figure 4.3). These data indicate that the neural representations of numbers for both formats seem to be present on a large spatial scale and in all cortices.

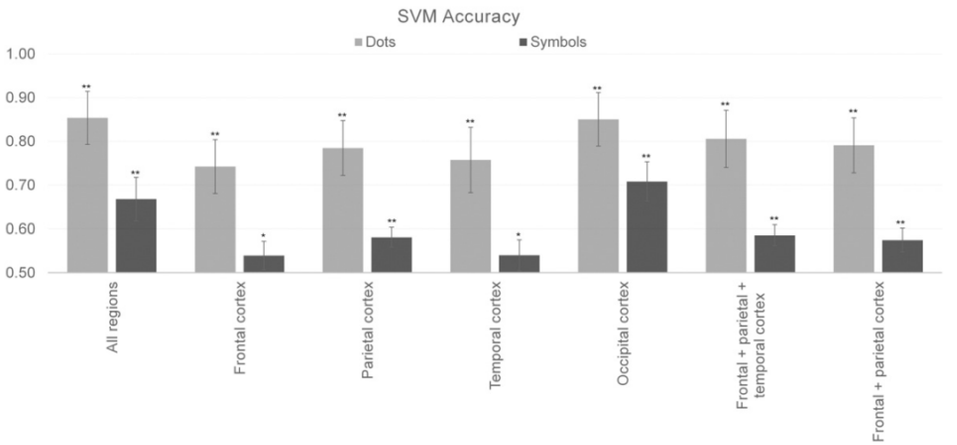

Figure 4.3: Significant decoding performances for symbolic and non-symbolic stimuli for the cortices, the error bars represent the standard error of mean (* $p < 0.05$ ** $p < 0.01$).

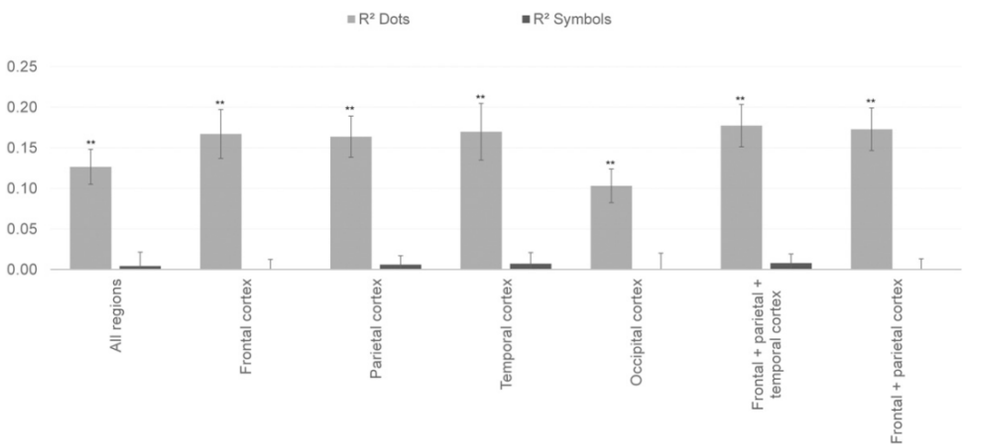

Figure 4.4: The distance effect of dots and symbols in the different cortices. The error bars represent the standard estimate of error (* $p < 0.05$ ** $p < 0.01$).

Neural distance effect To test whether the significant decoding of symbolic and non-symbolic magnitudes on a large spatial scale was due to the underlying magnitude of the stimuli, we applied a regression analysis to the decoding accuracies of those ROIs that showed significant decoding performance (Figure 4.4). For non-symbolic magnitudes all the cortices showed a significant distance effect: All regions ($R^2 = 0.13$, $p < 0.001$), frontal cortex ($R^2 = 0.17$, $p < 0.001$), parietal cortex ($R^2 = 0.16$, $p < 0.001$), temporal cortex ($R^2 = 0.0.17$, $p < 0.001$), occipital cortex ($R^2 = 0.10$, $p = 0.002$), frontal + parietal + temporal cortex ($R^2 = 0.18$, $p < 0.001$) and parietal + frontal cortex ($R^2 = 0.17$, $p < 0.001$). These results indicate that we captured magnitude related activity for non-symbolic magnitudes on a large spatial scale.

For symbolic magnitudes, there was no distance effect in any of the cortices: All regions ($R^2 = 0.004$, $p = 0.54$), frontal cortex ($R^2 = 0.0003$, $p = 0.87$), parietal cortex ($R^2 = 0.01$, $p = 0.47$), temporal cortex ($R^2 = 0.01$, $p = 0.43$), occipital cortex ($R^2 = 0$, $p = 0.96$), frontal + parietal + temporal cortex ($R^2 = 0.01$, $p = 0.41$) and parietal + frontal cortex ($R^2 = 0.0004$,$p = 0.85$). This all suggests that for symbolic magnitudes we did not capture any magnitude related activity on a large spatial scale.

Association digits and dots To investigate the invariance of the representation of magnitude across formats, we applied generalization pattern classification. For this, we trained the classifier to discriminate between two magnitudes in one format (for example between symbol 2 and symbol 4) and tested the performance of the classifier on discriminating between the same magnitudes in the other format (i.e., 2 dots and 4 dots). If a ROI contains an abstract representation of magnitude, one would expect that this representation gereralizes across different formats. The results for this analysis are summarized in Table 4.2.

There was no significant generalization from non-symbolic to symbolic magnitudes or from symbolic to non-symbolic magnitudes in any of the lobes, suggesting no representational overlap between both formats on a large spatial scale.

ROI	Dots to digits			Digits to dots		
	Accuracy	t[15]	p	Accuracy	t[15]	p
All Regions	0.49	-1.20	0.87	0.51	0.51	0.31
Frontal, Parietal & Temporal Cortex	0.49	-0.94	0.87	0.52	1.14	0.14
Frontal & Parietal Cortex	0.49	-0.87	0.80	0.50	-0.02	0.51
Frontal Cortex	0.50	-0.33	0.63	0.50	0.13	0.45
Parietal Cortex	0.49	-1.12	0.86	0.49	-0.70	0.75
Temporal Cortex	0.50	0.09	0.46	0.51	0.67	0.26
Occipital Cortex	0.49	-0.94	0.82	0.51	1.02	0.16

Table 4.2: Overview of the generalization results for generalization from dots to digits and from digits to dots.

Symbolic and non-symbolic representations: relevant ROIs in the lobes

To look further within the cortices, we selected a series of ROIs in the different lobes based on previous numerical cognition literature (see Methods, Regions of Interest). This was done to test whether numerical magnitude representations, a neural distance effect and a possible association between dots and digits can be observed on an intermediate spatial scale.

Decoding accuracies The decoding accuracies of the ROIs are summarized in Figure 4.5. For non-symbolic magnitudes, the classifier was able to discriminate between the different numbers of dots better than chance level in all the ROIs tested, except for the visual word form area.

The SVM results for symbolic magnitudes were, however, different. We observed significant decoding accuracy for classifying symbols in the left superior parietal lobule, inferior occipital cortex, fusiform gyrus, right superior frontal gyrus. However, we did not find a significant decoding accuracy in the IPS and in its different subdivisions: left anterior IPS, right anterior IPS, left posterior IPS and right posterior IPS. Together with the results on a large spatial scale, these results suggests that in order to discriminate between the neural patterns of symbols one needs a lot of information which seems to be distributed throughout the brain.

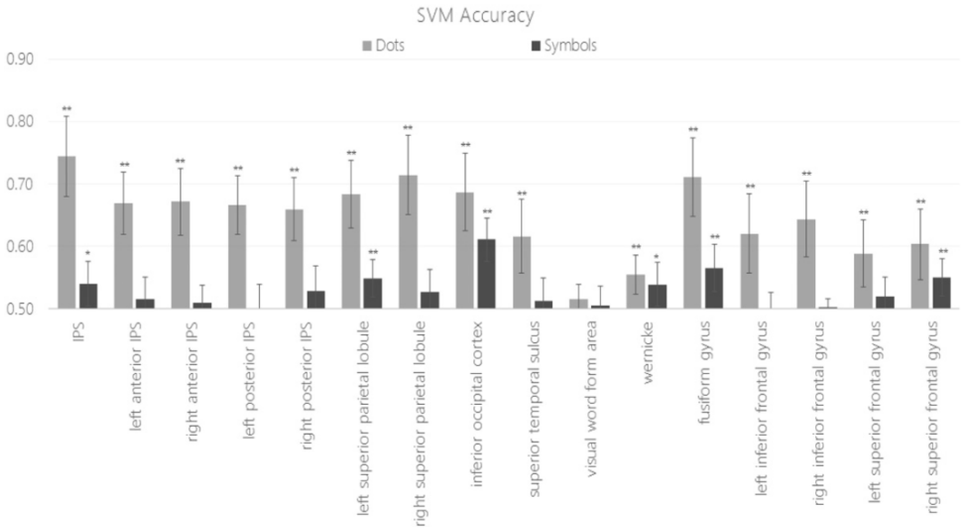

Figure 4.5: Significant decoding performances for symbolic and non-symbolic stimuli for ROIs on an intermediate spatial scale. The error bars represent the standard error of mean (* significant with FDR-correction ($q = 0.05$) for multiple comparisons; $\sim$ significant if no FDR-correction is applied).

Neural distance effect Results for the neural distance effect of symbolic and non-symbolic magnitudes are summarized in Figure 4.6. For non-symbolic magnitudes, most regions had a significant distance effect: IPS ($R^2 = 0.12, p < 0.001$), left anterior IPS ($R^2 = 0.06, p < 0.02$), right anterior IPS ($R^2 = 0.05, p < 0.02$), left posterior IPS ($R^2 = 0.12, p < 0.001$), right posterior IPS ($R^2 = 0.19, p < 0.001$), left superior parietal lobule ($R^2 = 0.16, p < 0.001$), right superior parietal lobule ($R^2 = 0.24, p < 0.001$), inferior occipital cortex ($R^2 = 0.11, p < 0.001$), superior temporal sulcus ($R^2 = 0.05, p = 0.03$), fusiform gyrus ($R^2 = 0.16, p < 0.001$), left inferior frontal gyrus ($R^2 = 0.11, p < 0.001$), right inferior frontal gyrus ($R^2 = 0.09, p < 0.001$) and right superior frontal gyrus ($R^2 = 0.09, p = 0.01$). Only two ROIs that showed significant decoding accuracy, did not demonstrate a significant distance effect: Wernicke's area ($R^2 = 0.02, p = 0.21$) and the left superior frontal gyrus ($R^2 = 0.01, p = 0.38$). This suggests that the significant decoding of non-symbolic magnitudes in these two areas was not related to magnitude.

For symbolic magnitudes, there was no distance effect in any of the ROIs that showed significant decoding accuracy: left superior parietal lobule ($R^2 = 0.003, p = 0.62$), inferior occipital cortex ($R^2 = 0.0003, p = 0.86$), $p = 0.13$), fusiform gyrus ($R^2 =$

0.02, $p = 0.16$) and right superior frontal gyrus ($R^2 = 0.01$, $p = 0.30$). Thus, we did not find any magnitude related activity in the ROIs tested on a large and intermediate spatial scale for the symbolic magnitudes.

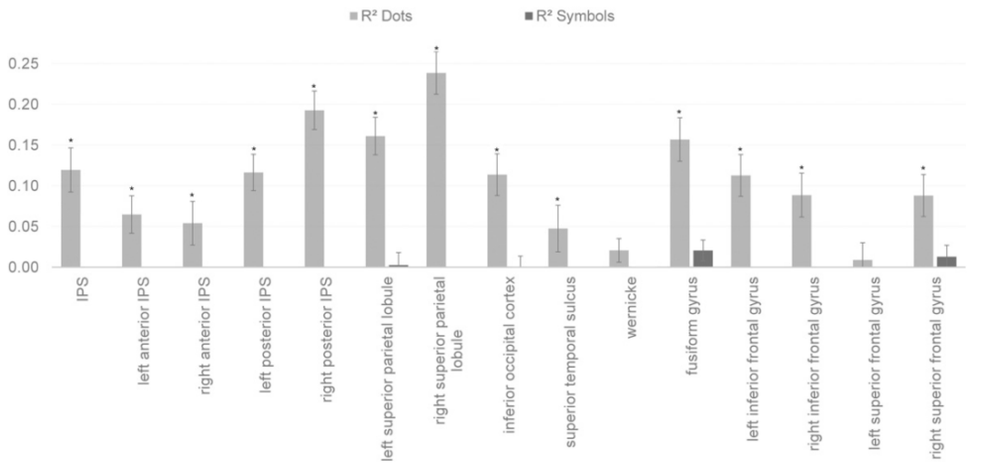

Figure 4.6: Significant decoding performances for symbolic and non-symbolic stimuli for ROIs on an intermediate spatial scale. The error bars represent the standard error of mean (* significant with FDR-correction ($q = 0.05$) for multiple comparisons).

Association digits and dots We again tested the neural representational overlap between symbolic and non-symbolic magnitudes in the abovementioned ROIs by applying generalization SVM. Similar to the large scale analyses, we did not find any generalization from symbolic to non-symbolic magnitudes or from non-symbolic to symbolic magnitudes.

Results on a small spatial scale: searchlight analysis (SLA)

A searchlight analysis is ideal for finding where on a local spatial scale (a) the neural patterns for stimuli in symbolic and non-symbolic formats are distinguishable (b) where the neural patterns of both formats represent a magnitude and (c) if there is any overlap between symbolic and non-symbolic representations.

We applied a whole-brain SLA with a radius of twice the voxel size resulting in a 'searchlight cluster' of 33 voxels. This analysis resulted in two maps with decoding accuracy (symbolic and non-symbolic magnitudes), two maps with the distance effect

(symbolic and non-symbolic magnitudes) and two maps with generalization accuracy (from symbolic to non-symbolic and from non-symbolic to symbolic magnitudes) for each subject. These resulting maps were submitted to a group analysis and corrected for multiple comparisons (Figure 4.7).

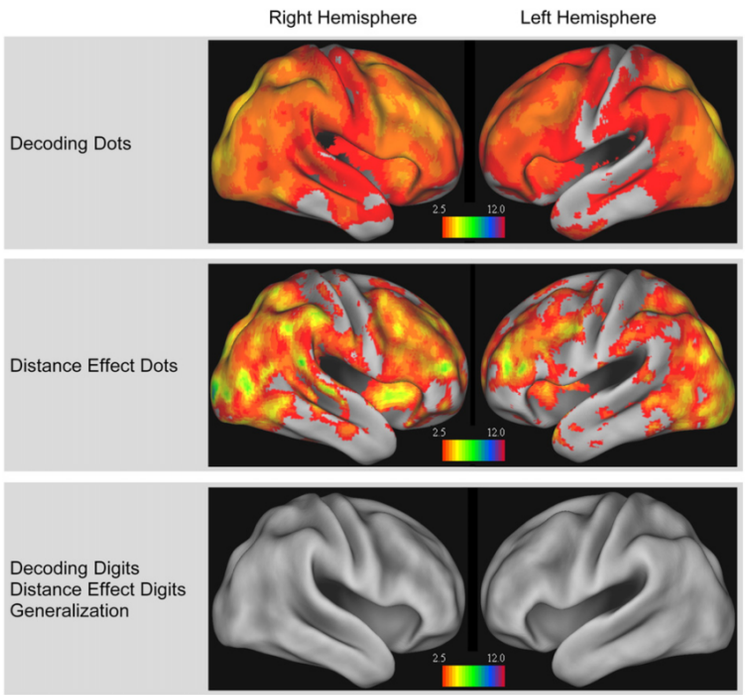

Figure 4.7: Results of the whole-brain searchlight analysis for FDR-corrected threshold of $t = 2.5$.

Decoding SLA For both symbolic and non-symbolic magnitudes the SLA confirmed the results from the decoding analyses. The neural representations of non-symbolic magnitudes seemed to be present throughout the brain and on a very local spatial scale. For the symbolic magnitudes, we observed no representational information on a local spatial scale, which suggests that the relatively low decoding accuracies in the ROI analysis relied on the inclusion of a large number of individually defined voxels.

Neural distance effect The SLA for the neural distance effects of non-symbolic magnitudes revealed that in most regions with significant decoding accuracies there was a neural distance effect. This results corresponds to the ROI-based neural distance effect analysis. For symbolic magnitudes, the SLA did not reveal any magnitude

related activity on a local spatial scale in the cortex, also confirming the ROI-based neural distance effect analysis.

Association digits and dots Concerning the ROI-based generalization analysis, the SLA also confirmed the absence of an abstract representation on a local spatial scale as there was no generalization from symbolic to non-symbolic and from non-symbolic to symbolic magnitudes.

Correlations between behavioral and imaging data

It has been suggested that reaction time differences between conditions in a comparison task are correlated with the brain activity of those conditions (Pinel et al., 2001b), suggesting an effect of task difficulty on brain activity. We therefore correlated the difference (symbolic non-symbolic magnitudes) in reaction time between formats with the difference in decoding between formats. This was done for the All Regions and parietal cortex, because we had no a priori hypothesis for the specific area where this correlation would emerge. In All Regions there was a significant negative correlation (r = -0.51, p = 0.04) while in the parietal cortex a non-significant negative correlation was observed (r = -0.45, p = 0.08). As these correlations are negative, pointing to higher decoding when the reaction is longer, they do not reflect effects of task difficulty, but rather indicate how much attention and processing was needed by the subject to deal with the stimuli.

We have also correlated the behavioral distance effect (based on reaction times, as explained above) with the neural distance effect in All Regions and parietal cortex. This correlation was significant for non-symbolic magnitudes (r = 0.51, p = 0.046) in All Regions and not significant (r = 0.16, p = 0.553) in the parietal cortex. We found no significant correlation between the behavioral distance effect and the neural distance effect of symbolic magnitudes in All Regions ($r = 0.30, p = 0.27$) and parietal cortex (r = 0.18, p = 0.50). The latter could be explained by recourse to the failure to observe a neural distance effect for symbolic magnitudes in the All Regions and parietal cortex.

4.4 Discussion

The present study was conducted to identify neural correlates underlying symbolic and non-symbolic magnitude processing. In contrast to the existing body of studies that mainly used univariate fMRI methods to probe this question, we applied MVPA to unravel the neural activity patterns of numerical magnitudes. To the best of our knowledge, only two studies have applied this technique before, i.e. Eger et al. (2009) and Damarla & Just (2012). However, these two studies restricted the focus of their analyses to the entire parietal cortex without examining any smaller regions of interest inside and outside the parietal cortex. Extending these two studies, we applied MVPA outside the parietal cortex and ran these analyses on three spatial scales: a large scale (the entire cortex, frontal cortex, parietal cortex, temporal cortex and occipital cortex), an intermediate scale with 16 ROIs throughout the whole cortex and a local scale by applying a whole brain searchlight analysis.

In summary, we found different neural patterns for non-symbolic compared to symbolic magnitudes. For dot arrays, most brain regions showed a neural distance effect, indicating a widespread representation of numerical magnitude for dot arrays. By contrast, symbolic magnitudes were only distinguishable when entire lobules were used as ROIs, and in some smaller ROIs (left superior parietal lobule, inferior occipital cortex, fusiform gyrus and right superior frontal gyrus), albeit with lower decoding accuracy. This pattern of results indicated that the neural representations of symbolic magnitudes were widely distributed across the entire cortex. No evidence was found for a neural distance effect of symbolic magnitudes in our data. The generalization analyses revealed no overlapping representations for digits and dots in any of the selected regions of interest. Results from the ROI-based MVPA analysis were extended by a whole-brain searchlight analysis, which yielded the same results. In all, these data are very hard to reconcile with an abstract representation of numerical magnitude.

4.4.1 Representations of symbolic and non-symbolic magnitudes are not restricted to only the parietal cortex

In contrast to previous MVPA studies that limited their scope to the parietal cortex, the present study is the first study to apply MVPA to the entire cortex, the individual lobes and 16 ROIs for decoding symbolic and non-symbolic magnitudes. Concerning the parietal cortex, we found significant decoding performances for both symbols and dot arrays, which is in accordance with Eger et al. (2009) and Damarla & Just (2012). However, we also observed significant decoding for both formats in the frontal, occipital and temporal cortices, suggesting the presence of neural representation of symbolic and non-symbolic magnitudes on a large spatial scale in the entire cortex. Our results indicate that only looking at the parietal cortex shows a small part of the story. Because there are no previous numerical cognition MVPA fMRI studies looking at other ROIs besides the entire parietal cortex, we cannot directly compare the current results with previous MVPA data.

The existing univariate and adaptation fMRI studies pinpointed the IPS as the number module in the brain, against the background of similar neural effects for symbolic and non-symbolic magnitudes (Dehaene et al., 2003; Fias et al., 2003; Piazza et al., 2007). We found significant decoding accuracies for dots in the IPS, suggesting the presence of distinctive neural patterns for non-symbolic magnitudes in the IPS. However, this was not observed for symbolic magnitudes.

More crucially, we also applied MVPA to other ROIs besides the IPS and outside the parietal cortex. Our results show the decoding of both formats outside the IPS, with significant decoding performances for dots in regions in the frontal, occipital and temporal cortices. For symbolic stimuli, we observed significant decoding in the fusiform gyrus, right superior frontal gyrus, left superior parietal lobule, and inferior occipital cortex. This suggests that the neural representations of symbolic and non-symbolic magnitudes are not restricted to the IPS or the parietal cortex.

In this context caution is needed when interpreting the nature of these representations across the entire brain. It is most likely that the representations of dots and symbols in, for example, the inferior occipital cortex are more related to the visual properties of the stimuli than to their numerosity. This is in line with (Gebuis & Reynvoet, 2012a) who showed that the comparison of (non-symbolic) number also includes many non-numerical processing (e.g., perceptual, action, semantics). The parietal cortex, on the other hand, can be expected to contribute more than the other regions to representing magnitudes and numerositiy, while occipital regions are known to represent the visual properties of stimuli and prefrontal cortex might process task-related aspects (e.g. process small and large numbers differently). These non-numerical representations will probably contribute the most to the non-symbolic numbers because there is little decoding in the symbolic numbers across the ROIs.

4.4.2 Representations of dots and digits are different

Our findings suggest a divergence in the neural representations between symbolic and non-symbolic stimuli. First, in all the lobes we observed higher decoding performance for non-symbolic stimuli compared to symbolic stimuli. This higher decoding accuracy for dots versus digits was also found in the parietal cortex by Eger et al. (2009) and Damarla & Just (2012). Because we extended these two studies by not restricting MVPA to the entire parietal cortex, the current data indicate that the higher decoding performance for dots versus digits is seen not only in the parietal cortex, but also in the other lobes.

A possible explanation for this finding might be that the symbols (digits) share more features than dot patterns. Although being different in magnitude, the symbol '2' and '8' share many visual characteristics, such as being one visual symbol and being processed in the same way (reading). In contrast, these visual characteristics are very different between 2 and 8 dots, and these dot patterns might processed in different ways: 2 dots are processed in an exact way, whereas 8 dots might be approximated.

The different decoding results for symbolic and non-symbolic magnitudes could be explained in the light of recent findings by Shum et al. (2013). They used intracranial electrophysiological recordings in epileptic patients and reported higher activation for Arabic digits compared with letters, false fonts, number words and non-number words in the inferior temporal gyrus. Their study suggested one location that was very specific for processing Arabic digits. However, this regions falls in the fMRI signal-dropout zone, thus we cannot capture the functional response for symbolic magnitudes in this region with fMRI.

Although we cannot exclude the possibility of a symbolic number region outside the range of fMRI, we still found significant decoding accuracies for symbolic magnitudes. This was not observed in one small region, but it was more scattered throughout the entire cortex, suggesting that the neural representations of digits are embedded on a large spatial scale. This finding is in line with Eger et al. (2009) who reported the absence of neural representations for symbolic magnitudes on a relatively local spatial scale in the parietal cortex in contrast to distinguishable neural patterns on a large spatial scale in the parietal cortex.

In accordance with the studies of Eger et al. (2009), Damarla & Just (2012) and Shum et al. (2013), the present study suggests different processing in different locations of non-symbolic and symbolic stimuli. These neuroimaging studies converge nicely with previous behavioral studies showing differences between both formats. For example, Lyons et al. (2012) demonstrated that cross-format number comparisons were more difficult than within-format number comparisons, which suggests that symbolic and non-symbolic magnitudes are independently processed.

4.4.3 The neural distance effect for symbolic and non-symbolic magnitudes is different

To test whether the decoding performances found in the ROIs were reflecting a magnitude representation, we verified whether a neural distance effect could be found

in these regions. In line with previous studies, we observed the presence of a neural distance effect for non-symbolic magnitudes and an absence of this effect for symbolic magnitudes in the parietal cortex (Damarla & Just, 2012; Eger et al., 2009). We extended our scope to ROIs in the parietal, frontal, temporal and occipital cortices and found magnitude representations for dot arrays in most ROIs. However, we did not find magnitude representations for symbols in any of our ROIs (large and intermediate spatial scale), including the IPS, even though the number comparison task demanded an explicit magnitude judgment. This suggests that, in contrast to non-symbolic magnitudes the neural activation in the IPS for symbolic magnitudes is not related to the underlying magnitude.

Despite this differences in the neural distance effects of dots and digits, we observed a behavioral distance effect for both symbols and dots. However, the mere presence of a behavioral distance effect does not necessarily indicate similar underlying cognitive processes in dealing with symbolic and non-symbolic stimuli. For example, Lyons et al. (2012) showed that in the presence of behavioral distance effects for digits and dots in a number comparison task, format number comparisons were more difficult, which suggests different cognitive processes for symbolic and non-symbolic magnitudes. Also, Campbell (1994); Dehaene & Akhavein (1995); Ganor-Stern & Tzelgov (2008) observed interactions between numerical distance and format, indicating that different cognitive processes are involved in symbolic and non-symbolic tasks. Maloney et al. (2010) observed no correlation between the distance effect of dots and symbols, suggesting different underlying mechanisms for both formats. In line with this, the present study did not observe a correlation between the behavioral distance effect of digits and dots.

4.4.4 Relationship between symbolic and non-symbolic magnitudes

We found no overlapping neural patterns for symbolic and non-symbolic magnitudes in any of the ROIs, suggesting no representational overlap for both formats. This

result contradicts the study of Eger et al. (2009), which found a generalization from digits to dots (57%), but no generalization from dots to digits. Eger et al. (2009) explained these results in the context of a neural network model constructed by Verguts & Fias (2004). This network model suggests that a subset of neurons that originally responds to non-symbolic magnitudes acquires selectivity to the corresponding symbolic number and, while preserving response selectivity to non-symbolic magnitudes, becomes more narrowly tuned to the specific symbolic number.

However, Damarla & Just (2012) were not able to replicate the data by Eger et al. (2009) and reported that their poor generalization across formats suggests that the neural representation of numerical magnitudes in the parietal areas is primarily format-specific. On top of that, Eger et al. (2009) did not find any generalization in their parietal cortex searchlight analysis. In line with this, we also did not find any generalization in the whole brain searchlight analysis. Note that our study is very similar to the study of Eger et al. (2009), and that our study had an appropriate sensitivity (we were able to decode each of the two formats) and reasonable power (16 subjects). Against this background, it seems appropriate to conclude that no detectable overlapping representations between symbolic and non-symbolic magnitudes are present, neither in the parietal cortex nor in the cortex as whole.

4.4.5 Whole-brain searchlight analysis

This study is the first to apply a whole brain searchlight analysis in the context of decoding symbolic and non-symbolic magnitudes. With this analysis, we aimed to detect a neural distance effect for both formats, and tested the representational overlap between digits and dots. The whole brain searchlight analysis resulted in an accurate decoding and neural distance effect for dots in most parts of the cortex, which suggests a very local representation of non-symbolic magnitude in the brain. A small spherical region at many cortical positions is sufficient to decode the number of dots that is shown to the participants. For the symbolic stimuli no significant decoding and neural distance effect on a local scale was found. Together with the ROI-based MVPA

analysis, this suggests that symbolic stimuli are represented in a very distributed manner across the entire brain and need the inclusion of a large number of individually defined voxels to detect their neural pattern.

4.4.6 Is there an abstract representation of magnitude in the brain?

The majority of the studies concerning numerical cognition have suggested that a domain-specific number module is present in the IPS (Ansari, Dhital & Siong, 2006; Cohen Kadosh et al., 2005; Eger et al., 2003; Fias et al., 2003; Piazza et al., 2007; Pinel et al., 2004). Although the results of these studies are seen as evidence for the domain-specificity of the IPS, Shuman & Kanwisher (2004) challenged the conclusions drawn from these studies based on three fMRI experiments. These authors did not find an adaptation effect for repeated numerosities in different formats, but observed less strong activations for number tasks than for color tasks in the IPS. They also showed that the IPS responded more strongly to difficult compared to easy tasks with no differences between number tasks and color tasks. Hence, the experiments of Shuman & Kanwisher (2004) do not support the hypothesis of the IPS as a domain-specific area for abstract number processing.

Turning to our study, if such abstract representation would exist one should find: (a) similar decoding results for both symbolic and non-symbolic magnitudes, (b) similar neural distance effects for both formats and (c) a representational overlap between symbols and dot arrays. In contrast to this, we found (a) different decoding results for digits and dots with major differences for the location of neural representations for both formats; (b) differences in the presence of the neural distance effects between digits and dots; and (c) no generalization effects from digits to dots and vice versa, which indicates no representational overlap between dots and digits. This pattern of findings was observed on a large spatial scale (entire cortices), an inter-mediate spatial scale (regions of interest) and a small spatial scale (whole-brain searchlight with a radius of twice the voxel size) and is hard to reconcile with the existence of an

abstract magnitude representation.

4.5 Conclusion

We confirm the conclusion of Eger et al. (2009) that MVPA allows one to distinguish the representations of different numerical magnitudes with a higher accuracy for dot patterns than for symbols. However, in our study the numerical representations were format-dependent without any common format-independent representation of magnitude: Classifiers trained on dot patterns were not able to generalize to symbols (or vice versa). Although subjects were performing a magnitude-related task showing a distance effect at the behavioral level, the MVPA results showed a distance effect for non-symbolic but not for symbolic stimuli. The searchlight analyses did not reveal any overlapping representations between both formats anywhere in the cortex. These findings are hard to reconcile with the idea of an abstract representation of numerical magnitudes.

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5 Symbolic and non-symbolic representations as objects in parietal cortex

The contributions of the first author are:

- Literature study
- Development of the code for the classification algorithms of empirical data
- Development of the code for confusion analysis of empirical data
- Collecting empirical data
- Perform all analyses
- Co-interpretation of empirical results
- Co-formulation of conclusions
- Text redacting

Published as

Bulthé, J., De Smedt, B., & Op de Beeck, H. P. (2015). Visual Number Beats Abstract Numerical Magnitude: Format-dependent Representation of Arabic Digits and Dot Patterns in Human Parietal Cortex. Journal of Cognitive Neuroscience, 27(7), 1376-1387.

Abstract

In numerical cognition, there is a well-known but contested hypothesis that proposes an abstract representation of numerical magnitude in human IPS. On the other hand, researchers of object cognition have suggested another hypothesis for brain activity in IPS during the processing of number, namely that this activity simply correlates with the number of visual objects or units that are perceived. We contrasted these two accounts by analyzing multivoxel activity patterns elicited by dot patterns and Arabic digits of different magnitudes while participants were explicitly processing the represented numerical magnitude. The activity pattern elicited by the digit ”8” was more similar to the activity pattern elicited by one dot (with which the digit shares the number of visual units but not the magnitude) compared to the activity pattern elicited by eight dots, with which the digit shares the represented abstract numerical magnitude. A multivoxel pattern classifier trained to differentiate one dot from eight dots classified all Arabic digits in the one-dot pattern category, irrespective of the numerical magnitude symbolized by the digit. These results were consistently obtained for different digits in IPS, its subregions, and many other brain regions. As predicted from object cognition theories, the number of presented visual units forms the link between the parietal activation elicited by symbolic and nonsymbolic numbers. The current study is difficult to reconcile with the hypothesis that parietal activation elicited by numbers would reflect a formatindependent representation of number.

5.1 Introduction

Researchers in the field of numerical cognition have proposed that the IPS contains an abstract module for number processing, which means that the IPS comprises neural representations for numerical magnitudes that are independent of format (e.g. Arabic digits or dot patterns). Such an abstract representation account assumes that,

for example, the Arabic digit '4', is represented in the same way as a pattern of 4 dots, activating the same neurons, but this representation is different from Arabic digit '8' and a pattern of 8 dots. This conclusion is drawn from many studies who observed that the IPS is involved in magnitude processing and that this IPS activity is independent of format (Dehaene & Cohen, 1997; Eger et al., 2003; Naccache & Dehaene, 2001; Pinel et al., 2001a).

Many of the relevant brain imaging studies, however, have at least one of the following two major limitations, which undermine the observed evidence of IPS as an abstract number module. The first limitation deals with the exclusive use of Arabic digits and/or number words (e.g. 'two') to unravel the abstractness of number processing in the parietal cortex, which makes it difficult to make comparisons with the processing of a non-symbolic numerical magnitude, such as dot patterns (Cohen Kadosh & Walsh, 2009b; Shuman & Kanwisher, 2004). When both symbolic and non-symbolic numbers are used in the task, there is less support for the existence of an abstract representation of numbers (Ansari, Fugelsang et al., 2006; Shuman & Kanwisher, 2004).

Second, the notion of abstract number processing predicts null results in neuroimaging studies that compare the mean BOLD signal for Arabic digits and dots in the IPS. More specifically, these studies predict no significant differences in the mean activation between different formats in the IPS. Such null results are, however, hard to interpret because they might have been due to a lack of statistical power, or to the insensitivity of the paradigms that were used (Cohen Kadosh & Walsh, 2009b).

Researchers have tried to address this latter limitation by using adaptation fMRI paradigms. In this paradigm, the repetition of the same stimulus (e.g. Arabic digit 4) reduces the BOLD signal. If the adapted BOLD signal changes when the stimulus magnitude changes but not when the stimulus format changes (e.g. four dots), then the inference is made that the underlying neuronal population is sensitive to stimulus magnitude and not to format. This paradigm has allowed researchers in the field of

numerical cognition to test whether there are abstract number neuronal populations or not (Holloway et al., 2013; Nieder, 2009; Piazza et al., 2004b, 2007; Roggeman et al., 2011; Santens et al., 2010; Shuman & Kanwisher, 2004).

The use of adaptation fMRI did not resolve the discussion about the presence of abstract representations of numerical magnitudes in the human parietal cortex. For example, the adaptation study of Piazza et al. (2007) with Arabic digits and dots demonstrated that the BOLD signal in the right IPS recovered when the numerical magnitude changed and, that this recovery was not affected by the stimulus format of the test stimulus. This result fits with the idea of abstract numerical magnitude processing in the IPS. However, Piazza et al. (2007) also observed an interaction effect between format and recovery in the left IPS, which suggested format dependent processing of numerical magnitudes (Ansari, 2007; Cohen Kadosh & Walsh, 2009b). Together with other fMRI adaptation studies (Cohen Kadosh et al., 2007) and other fMRI evidence (Holloway et al., 2010), it seems more plausible that both format-independent and -dependent representations are present in the parietal cortex (Ansari, 2007), at least, as far as adaptation provides a reliable measure of neuronal selectivity, which is a point that has been contested (Sawamura et al., 2006).

Recently, fMRI studies have included a different methodology to assess neural selectivity, namely MVPA (see Norman et al. (2006)). MVPA might be a helpful tool to further explore where in the cortex overlapping and/or distributed representations of dots and Arabic digits are present (Ansari, 2008; Dehaene, 2009). Specifically, MVPA has the potential to reveal the presence of neural representations for dots and Arabic digits in the parietal cortex and IPS, and this technique allows one to straightforwardly test whether these neural representations are overlapping or not. For example, a classifier can be trained to differentiate between Arabic digit 2 and Arabic digit 4, and this same classifier can then be used to differentiate between two dots and four dots. If an abstract representation underlies parietal activity, this classifier should be able to generalize from Arabic digits to dots, or vice versa.

Recent studies applying this MVPA technique have been able to extract format-specific magnitude information in the parietal cortex and IPS (Bulthé, De Smedt & Op de Beeck, 2014; Damarla & Just, 2012; Eger et al., 2009), however the evidence for format-independent representations is weak. Damarla & Just (2012), and Bulthé, De Smedt & Op de Beeck (2014) found no generalization and thus no overlapping representations between Arabic digits and dots in the parietal cortex or the IPS, which contradicts the existence of an abstract representation of numerical magnitude in the parietal cortex or IPS. On the other hand, Eger et al. (2009) observed weak asymmetrical generalization between dots and digits: the discrimination of Arabic digits generalized to dots was just above chance level, but the generalization from dots to Arabic digits was at chance level. Overall, magnitude representations in IPS seem to a large degree to be format dependent.

However, format dependence does not necessarily mean that there is no relationship between how stimuli from different formats are represented, as the parietal cortex has not only been implicated in magnitude representations. Researchers of object cognition have shown that activity in the IPS is associated with the number of visual objects that are presented (Song & Jiang, 2006; Todd & Marois, 2005; Vogel & Machizawa, 2004; Wojciulik & Kanwisher, 1999; Y. Xu & Chun, 2007a; Y. Xu, 2008). From this object cognition literature one would predict that Arabic digits will have similar activity to one dot because both contain only one visual object. This prediction is not compatible with the hypothesis of an abstract magnitude representation, which would predict that an Arabic digit and a dot pattern that share the same numerical magnitude (e.g. digit 4 and 4 dots) would elicit a similar pattern of activity across the neurons in the IPS.

Against this background, the associations between the representations of Arabic digits and dots remain unclear. Are the neural patterns in the parietal regions of Arabic digits and dots more alike when they share an underlying magnitude, as expected from the numerical cognition literature (Dehaene, 2009; Nieder et al., 2002; Piazza et al., 2007)? Or, are the neural patterns of Arabic digits and dots more related

by the number of visual elements they share, as expected from studies in the field of object cognition (Song & Jiang, 2006; Todd & Marois, 2005; Vogel & Machizawa, 2004; Y. Xu & Chun, 2007a; Y. Xu, 2008)? The present study integrated both research fields (numerical cognition and object cognition) and tested their opposite predictions about the relative similarity of Arabic digits and dot patterns by using MVPA analyses.

5.2 Materials & Methods

Participants

Twelve healthy subjects (three male and nine female, 26.5 $\pm$ 2.28 years old, one left-handed) participated in this fMRI study and were paid for their participation. The participants had normal or corrected-to-normal vision and screening did not indicate a neurological or psychiatric history. The study was approved by the medical ethics committee of the KU Leuven. All participants provided written informed consent prior to scanning.

Stimuli

The stimuli (400 $\times$ 400 pixels) were presented in a white centered circle on a black background. Two formats were chosen, Arabic digits and dot patterns, and both comprised 1, 2, 4 and 8 as numerical magnitudes (Figure 6.1). Using the method and automated program by Dehaene et al. (2005), we controlled the dot stimuli for intensive confounding parameters, such as individual item size and inter-item spacing, and extensive confounding parameters, e.g. total luminance and total area spanned by the dots, by varying them randomly across the dot displays. To avoid adaptation for Arabic digits, the symbols varied in position and size across trials.

Stimuli were presented via Psychtoolbox 3 (Brainard, 1997) and a Barco 6400i LCD projector (resolution 1024 $\times$ 768, refresh rate 75 Hz) was used to project the stimuli on a vertical screen. The screen was positioned approximately 35 cm from subjects' eyes and was visible via a mirror attached to the head coil.

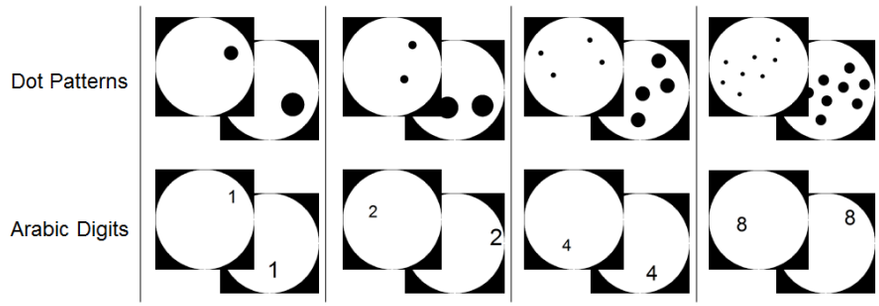

Figure 5.1: Stimulus examples for all four numerical magnitudes in both formats.

Design

The experimental procedures were very similar to a previous study (see Bulthé, De Smedt & Op de Beeck (2014) for more elaborated task details). The critical difference, introduced to be able to test the central hypotheses of the current article, was the inclusion of the numerical magnitude 1 in the present study. We used a short-block design with variable block duration of either 4, 5 or 6 seconds. One run lasted for 280 seconds and consisted of 48 experimental blocks (each condition was repeated 6 times, 2 times for each block duration) and 7 fixation blocks. In the experimental blocks, one condition (e.g., 4 dots) was repeated in 4, 5 or 6 trials. Each trial comprised in total 1000 ms, including 200 ms stimulus presentation and 800 ms fixation. The first and last fixation blocks were presented for 8 seconds. The fixation blocks between experimental blocks lasted either 4, 5 or 6 seconds. The experiment comprised 10 to 12 runs per participant. Brain imaging data were collected during a number comparison task, which made the participants explicitly access numerical magnitude representations (Piazza et al., 2004b; Pinel et al., 2004; Zorzi et al., 2011). Participants indicated whether the presented number was smaller or larger than 3 each time format and/or numerical magnitude changed.

The experiment also included a localizer task in which subjects had to perform a subtraction task. In this task, participants had to subtract numbers in the number domain 1 to 20 and they indicated whether the solution to a subtraction was odd or even. For each trial, the subtraction problem was presented for 1700 ms followed by

a fixation cross for 300 ms. The independent localizer data were used to define the regions of interest.

fMRI data acquisition

Data were acquired on a 3T Philips Intera Scanner (Department of Radiology, KU Leuven) with a 12-channel head coil. Functional images were obtained with a T2*-weighted EPI sequence with 48 oblique transverse slices, in-plane resolution 2.1 mm, slice thickness 2 mm, interslice gap .1 mm, TR = 3000 ms, TE = 30 ms, flip angle = 90, 104 $\times$ 104 matrix). For each participant, a high-resolution T1-weighted anatomical image was obtained (182 slices, resolution 0.98 $\times$ 0.98 $\times$ 1.2 mm, TR = 9.6 ms, TE = 4.6 ms, 256 $\times$ 256 acquisition matrix).

fMRI preprocessing

The data were processed with Statistical Parametric Mapping software package (SPM8, Welcome Department of Cognitive Neurology, London). Anatomical images were normalized to the standard brain template defined by the Montreal Neurological 152-brains average. Functional images were corrected for slice timing differences and realigned to the mean image to correct for head movements. Co-registration and spatial normalization were done using the parameters obtained in the normalization of the anatomical images. During normalization functional images were re-sampled to a voxel-size of 2 $\times$ 2 $\times$ 2 mm. Finally functional images were spatially smoothed using Gaussian kernels of 4 mm FWHM.

Statistical analysis

The experimental effects in each voxel were estimated by a multi-session design matrix that modeled the data at block level. A general linear model for each run was created with regressors for each participant for each condition. The six motion realignment parameters were additionally included as regressors of no interest to account for signal variations due to head movements. After fitting the general linear model for each run that was collected, subsequent analyses were performed using

t-statistics (which resulted from the contrast of each condition versus baseline), because they take both mean and variance of the activations into account (Misaki et al., 2010).

Regions of interest

For each ROI, we only included voxels that were significantly active in the contrast task minus fixation in the localizer scans. These voxels were restricted to those in the appropriate anatomical mask that was created with the anatomical WFU PickAtlas WFU PickAtlas Toolbox (Wake Forrest University PickAtlas, `http://fmri.wfubmc.edu/cms/software`), at least if the ROI was available in the toolbox. The functional contrast was thresholded at $p < 0.001$ (uncorrected for multiple comparisons).

In view of the literature reviewed above, we mainly focused on the parietal cortex, the IPS and its subdivisions (right and left anterior, and right and left posterior). In addition, we also included additional ROIs to find out whether similar effects were present in other brain regions (see Bulthé, De Smedt & Op de Beeck (2014) for a similar rationale). Selecting of ROIs were based on ROIs that have been reported to be involved in numerical processes in previous studies (Dehaene et al., 2003; Holloway et al., 2013; Lyons & Ansari, 2009; Maruyama et al., 2012; Piazza et al., 2007; Santens et al., 2010; Zago et al., 2001): All Regions (all voxels with significant activity versus baseline in the localizer task in a subject), frontal cortex, parietal cortex, temporal cortex, occipital cortex, left and right superior parietal lobule, inferior occipital cortex, superior temporal sulcus, visual word form area, Wernicke's area, fusiform gyrus, left and right inferior frontal gyri, and left and right superior frontal gyri.

For each subject, the 'All Regions' ROI was derived from the subtraction localizer task (i.e. the contrast 'task minus fixation') and comprised all voxels that survived the threshold at $p < 0.0001$. So, in this ROI all the voxels that processed and manipulated numerical magnitudes were included. The All Regions ROI was included because it gives a broad overview of the trends in the data (see for similar rationale

Bulthé, De Smedt & Op de Beeck (2014)). For example, when a specific ROI does not show any significant effects, the question remains whether there are just no effects present in that specific ROI or whether there are no measurable effects present in the entire cortex (in the first case the all regions ROI will show significant results; in the second case the all regions ROI will not yield any significant findings). It is important to point out that including the All Regions is not comparable to a searchlight analysis, because both analyses differ in their spatial scale. Searchlight analysis represents information on a local scale (a very small cluster of neighboring voxels), in contrast to the All Regions ROI which represents information distributed at global scale (Bulthé, van den Hurk et al., 2014). Figure 6.2 shows the All Regions ROI across subjects derived from a second level analysis.

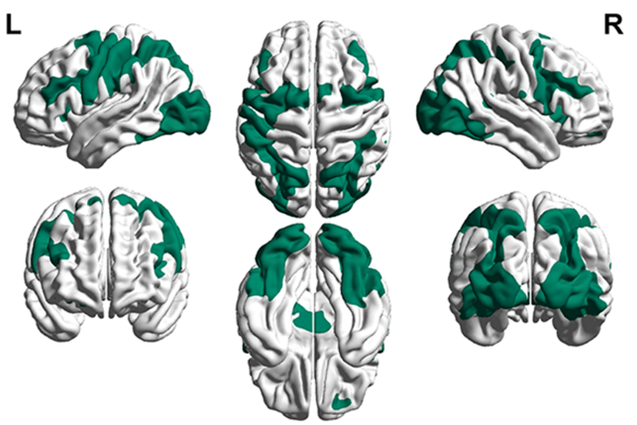

Figure 5.2: Included voxels in All Regions averaged across subjects which is derived from the localizer scans (constrast: subtraction task minus fixation). Multiple comparisons corrected with FDR = 0.05. BrainNet Viewer was used for visualization (Xia et al., 2013).

Data Analysis

We implemented decoding and generalization pattern classification with custom code written in Matlab. Both pattern recognition analyses were performed with SVM using the OSU SVM toolbox with the following parameters: a radial basis function kernel as decision function with parameter gamma set to 1; a C-SVC classification algorithm was used with parameter C set to 1. Response patterns for every condition

in each run were extracted for each ROI and normalized across voxels; the patterns were normalized by subtracting the mean across voxels and then dividing this by the standard deviation across voxels for each condition. We followed a repeated random sub-sampling cross-validation procedure: the data were randomly divided into 70% training data and 30% test data (the latter were averaged to one response pattern per condition) and this was repeated 100 times. The performance on the test data of all pairwise comparisons between conditions was averaged over different comparisons of interest (e.g. all comparisons of dot conditions, or all comparisons of Arabic digits).

Decoding

Decoding pattern classification resulted in a 7×8 decoding matrix for every ROI. Higher decoding accuracies indicate less similar neural representations. The decoding accuracies were then averaged over various comparisons of interest: Arabic digits (mean within-format decoding accuracy for Arabic digits), dots (mean within-format decoding accuracy for dots), same number (mean decoding accuracy of every dot condition contrasted with the Arabic digit of the same numerical magnitude), and different number (mean decoding accuracy of every dot condition contrasted with the Arabic digit of a different numerical magnitude). The within-format decoding results for every ROI were tested for significance ($p < 0.05$) across subjects by a two-sided *t*-test with respect to chance level (50%). The same number decoding accuracy was tested for significance ($p < 0.05$) against the different number decoding by a paired *t*-test.

Furthermore, the decoding accuracy was calculated between every Arabic digit condition (1, 2, 4, 8) with a particular dot condition (e.g., one dot) and averaged across those four decoding accuracies (Figure 5.5A). This resulted in four averaged decoding accuracies: decoding between digits and one dot, digits and two dots, digits and four dots, and digits and eight dots. A linear regression model was fitted to these four decoding accuracies, resulting in a slope which was tested for significance ($p < 0.05$)

across subjects by a *t*-test.

To rule out any bias in our decoding analysis that would lead to chance performance being higher than the theoretically expected proportion of 0.50, we performed random permutation tests (1000 permutations) for decoding of Arabic digits and dots, within the main ROIs: All Regions, parietal cortex and IPS. For both dots and Arabic digits, the 95% confidence interval of the null distribution was for all the regions within the range of [0.4929 - 0.5084].

Generalization

For generalization pattern classification, dot pattern condition pairs (e.g. 1 dot versus 4 dots) were used to train the classifier and the corresponding Arabic number conditions (e.g. Arabic digit 1 and Arabic digit 4) were used to test the performance of the classifier (Figure 5.3A). All pairs in this generalization analysis included the numerical magnitude '1' as one condition and one of the other numerical magnitudes as the contrast condition. From this analysis, three measures were extracted: the classification accuracy, the correct classification of Arabic digit 1 as one dot, and the confusion classification that indicates how many times another digit is classified as one dot (e.g. Arabic digit 4 classified as one dot). The generalization results for every ROI were tested for significance ($p < 0.05$) across subjects by two-sided *t*-tests with respect to chance level (50%).

5.3 Results

5.3.1 Behavioral results

A two-way repeated-measures (distance $\times$ format) ANOVA was applied to the accuracy and reaction times of the number comparison task for Arabic digits and dots. For accuracy, there was no significant main effect of either format ($F_{1,11}$= 3.88, p = 0.08) and distance ($F_{2,22}$= 1.88, p = 0.18) and there was no significant interaction between distance and format ($F_{2,22}$= 1.04, p = 0.18). For the reaction times, there was a sig-

nificant main effect for distance ($F_{2,22}$= 7.38, p = 0.004) showing longer reaction times for smaller distances than for larger distances. Again, there was no significant main effect of format ($F_{1,11}$ = 3.51, p = 0.09) and no significant interaction between format and distance ($F_{2,22}$= 0.81, p = 0.46).

5.3.2 Classification within format

Previous MVPA fMRI studies have shown that the parietal cortex and IPS contain patterns of activity of dots and Arabic digits, which are informative about which numerical magnitude is represented in a particular format (Bulthé, De Smedt & Op de Beeck, 2014; Damarla & Just, 2012; Eger et al., 2009). We first replicated this finding of previous studies, as a significant decoding within each format is a prerequisite to find any potential associations between formats.

The classification accuracies for dots were significantly above chance ($p < 0.05$) in all ROIs (Figure 5.3): All Regions (86%, t_{11} = 15.19, $p < 0.0001$), parietal cortex (73%, t_{11} = 9.06, $p < 0.0001$), IPS (66%, t_{11} = 5.57, $p < 0.0001$), left anterior IPS (59%, t_{11} = 3.79, p = 0.003), right anterior IPS (56%, t_{11} = 2.73, p = 0.02), left posterior IPS (65%, t_{11} = 4.65, p = 0.001), and right posterior IPS (60%, t_{11} = 3.65, p = 0.004). This indicates that in all these ROIs there were distinguishable neural patterns for dots with different numerical magnitudes.

The neural patterns for Arabic digits with different numerical magnitudes were distinct in following ROIs (Figure 5.3): All Regions (67%, t_{11} = 5.44, $p < 0.0001$), parietal cortex (60%, t_{11} = 4.61, p = 0. 001), IPS (59%, t_{11} = 4.32, p = 0.001), left anterior IPS (56%, t_{11} = 3.43, p = 0.006), and right posterior IPS (55%, t_{11} = 2.30, p = 0.04). However, in the right anterior IPS (52%, t_{11} = 1.62, p = 0.13) and left posterior IPS (50%, t_{11} = -0.20, p = 0.85) there were no distinguishable neural representations present for Arabic digits.

These data are in overall agreement with the decoding accuracies obtained in pre-

vious research (Bulthé, De Smedt & Op de Beeck, 2014). Also in other parietal and non-parietal ROIs, the results were very similar to the findings of Bulthé, De Smedt & Op de Beeck (2014).

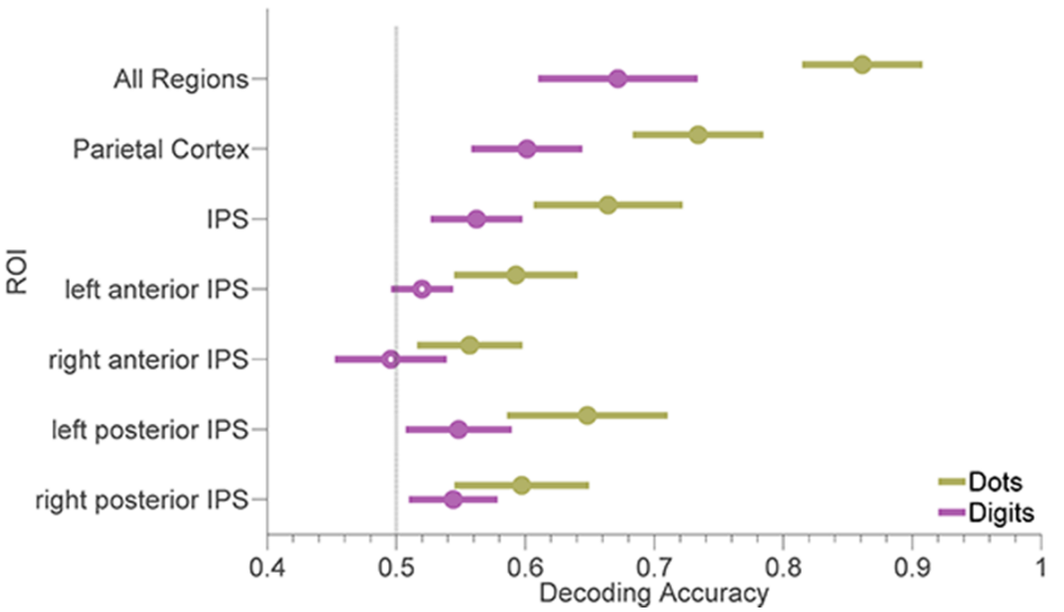

Figure 5.3: Within format decoding accuracies for dots and Arabic digits for every ROI are shown. Accuracies are obtained by averaging across all pairwise classifications within format. Error bars represent the 95% confidence interval. The colored filled bullets represent significant decoding ($p < 0.05$).

5.3.3 Classification between formats

In this analysis, we compared the activation patterns of Arabic digits and dots to test for their similarity. If an abstract representation underlies the numerical representations, we would expect a lower decoding accuracy (neural patterns are more similar, and thus less distinguishable) between Arabic digits and dots sharing the same numerical magnitude compared to Arabic digits and dots that do not have the same numerical magnitude. On the other hand, if the number of visual elements provides the important link between Arabic digits and dots, we expect an increase in decoding accuracies (e.g. neural patterns are less similar) between Arabic digits and a certain dot condition when more dots are visually presented.

The basic output of the decoding analyses were 7 $\times$ 8 matrices obtained by pairwise classification of the multi-voxel patterns of each condition with another condition (Figure 5.4). These decoding matrices represented the dissimilarity (e.g. higher decoding accuracies) of every condition with another condition. The dissimilarity matrices also allowed us to contrast the object cognition account, i.e. the number of visual units are the link between Arabic digits and dots, and numerical cognition account, i.e. numbers are represented in an abstract manner according to their magnitude.

Numerical cognition account

If number representations in IPS are abstract, we expect a lower decoding accuracy when an Arabic digit and a dot pattern share the same numerical magnitude than when they do not. In Figure 5.4, this would be visible by lower decoding accuracies in the four cells with the black squares compared to the other cells in the matrix. A visual inspection of the decoding matrix suggested that this was not the case: the four cells with a black square were on average as much or more distinguishable than the other cells in the matrix. This finding was quantified by the lack of any difference in the decoding accuracies between the 'same number' data (obtained by averaging the decoding accuracies of the pairwise comparisons of a dot and a digit condition sharing the same magnitude), and the 'different number' data (obtained by averaging the decoding accuracies of the pairwise comparisons of a dot and a digit condition with a different magnitude) in all of the ROIs, i.e. All Regions (t_{11} = 0.1406, p = 0.89), Parietal Cortex (t_{11} = -0.9563,p = 0.36), IPS (t_{11} = -0.1355, p = 0.89), left anterior IPS (t_{11} = 0.03, p = 0.97), right anterior IPS (t_{11} = 0.74, p = 0.47), left posterior IPS (t_{11} = -0.33, p = 0.75) and right posterior IPS (t_{11} = 0.17, p = 0.87). These results showed that the neural representations of Arabic digits and dots that shared the same numerical magnitude were as distinctive as Arabic digits and dots with different numerical magnitudes in the parietal cortex and in the IPS.

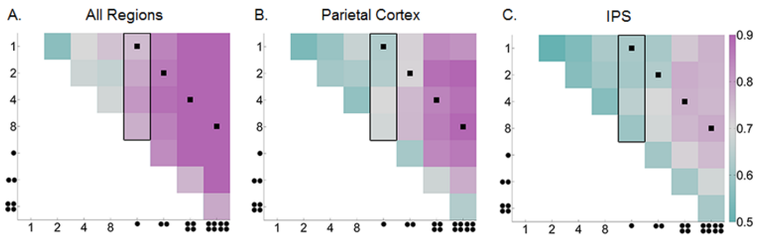

Figure 5.4: Decoding matrices for All Regions (**A**), Parietal cortex (**B**) and IPS (**C**). The cells with a black square represent each an Arabic digit and dot condition sharing the same numerical magnitude (relevant for the 'numerical cognition account'). The cells within the black outline are the decoding accuracies of the Arabic digits with one dot (relevant for the 'object cognition account'). The color bar represent decoding accuracies.

Object cognition account

According to the object cognition account, the pattern of activity in the IPS or parietal cortex to numerical stimuli should be related to the number of units contained in a stimulus. In this case, we expected a lower decoding accuracy (more similarity) when any digit was compared with one dot than with two dots, which might in turn result in a lower decoding accuracy to four dots, and so on. In the matrix, this would be visible by a lower decoding value in the black rectangle outline cells than in the columns to the right of this rectangle, and an increasing value (higher decoding accuracy) by each shift to the right in the matrix. A visual inspection of the similarity matrices in Figure 5.4 suggested that this was indeed the case: the similarities of the neural patterns between Arabic digits and one dot were higher than the similarities between a digit condition and dot conditions with more dots.

To test this more formally, a linear regression analysis was applied to the averaged decoding accuracies between Arabic digits and a certain dot condition (e.g. Arabic digits with one dot was calculated by averaging the decoding accuracy between Arabic digit 1 and one dot, the decoding accuracy between Arabic digit 2 and two dots, etc.). Concretely, the 4 numbers involved in the regression analysis corresponded to the mean of the cells surrounded by the black outline in the matrices shown in Figure 5.4, followed by the mean of the four cells in the next matrix column to the right, and so on until the last column in the matrices (Figure 5.5A).

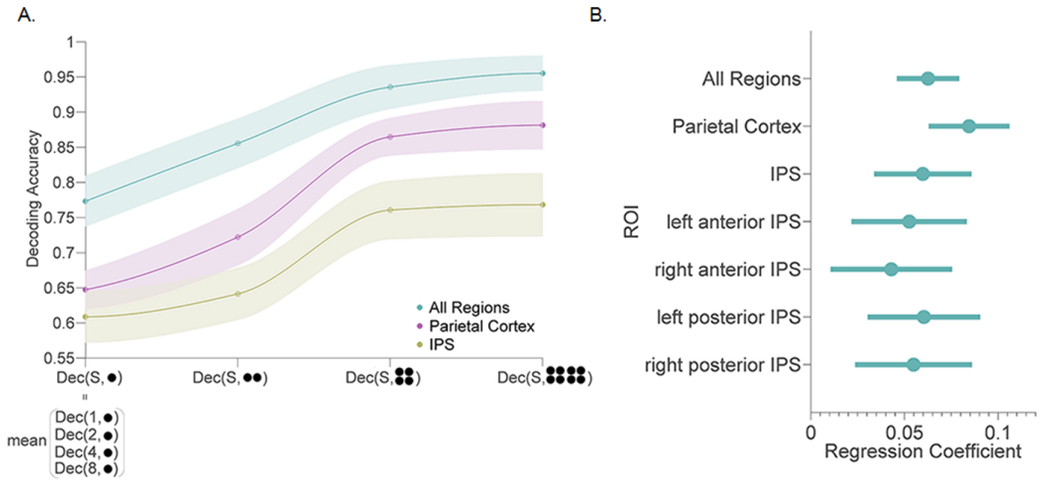

Figure 5.5: **A.** Four decoding measures for the association of the Arabic digits with a certain dot condition were calculated by the average of the decoding accuracies of each digit with a dot condition. The average data for each of the three main ROIs are shown. The filled areas represent the 95% confidence interval. The 'S' is an abbreviation for symbolic, and comprises all Arabic digit conditions. The lines connecting the data points and the continuous confidence intervals are for visualization purposes. **B.** The size of the slope (regression coefficient) of the linear regression applied to four possible decoding measures between the symbolic numbers and a certain dot condition. The error bars represent the 95% confidence interval. All of the slopes were significantly different from zero ($p < 0.05$).

The object cognition account predicts a positive slope as the neural response patterns are expected to reflect the number of objects on the screen. The number account does not predict a particular trend in this regression analysis, because only a low decoding accuracy between Arabic digits and dot patterns that share the same numerical magnitude is expected. The slopes of this linear regression analysis for all ROIs are illustrated in Figure 5.5B: All Regions ($t_{11} = 7.38$, $p < 0.0001$, $R^2 = 0.86$), Parietal Cortex ($t_{11} = 7.69$, $p < 0.0001$, $R^2 = 0.76$), IPS ($t_{11} = 4.51$, $p = 0.0004$, $R^2 = 0.56$), left anterior IPS ($t_{11} = 3.35$, $p = 0.003$, $R^2 = 0.60$), right anterior IPS ($t_{11} = 2.59$, $p = 0.01$, $R^2 = 0.50$), left posterior IPS ($t_{11} = 3.94$, $p = 0.001$, $R^2 = 0.48$) and right posterior IPS ($t_{11} = 3.45$, $p = 0.002$, $R^2 = 0.68$). In all the other defined ROIs this slope was significantly (all *ps* < 0.05) different from zero and positive, except for the visual word form area and left superior frontal gyrus where the same trend towards a positive slope was present but not significant.

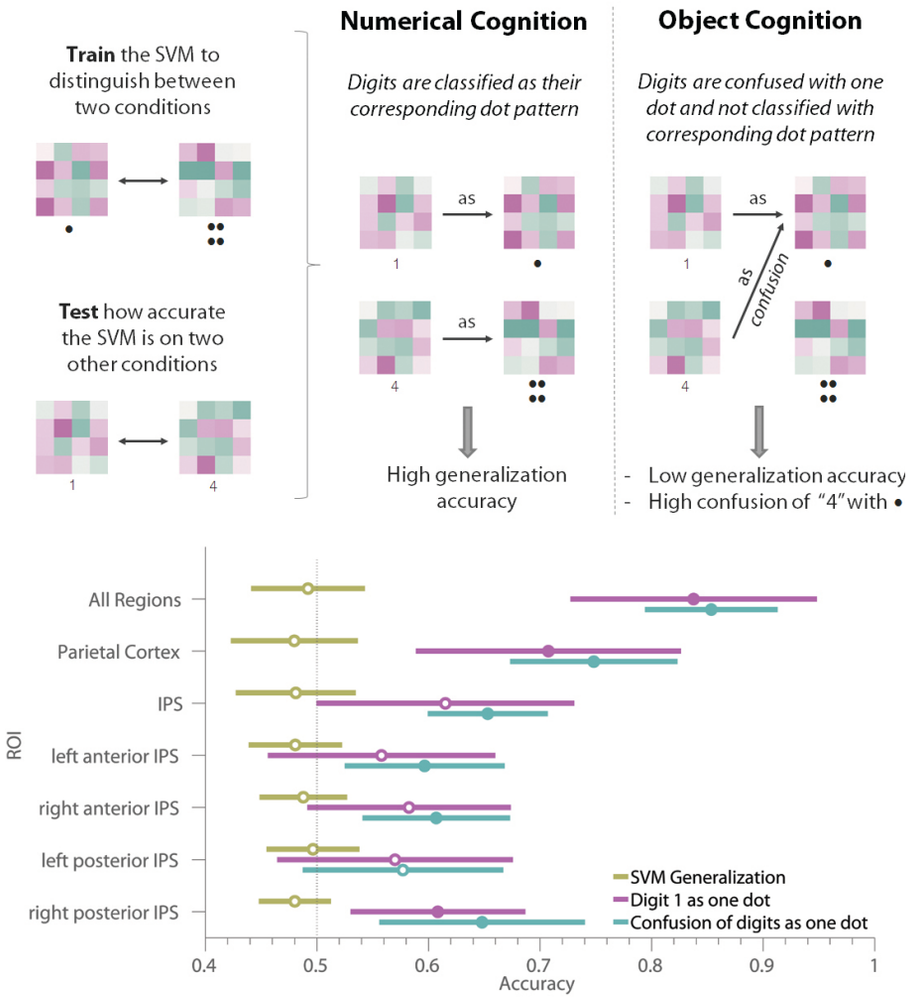

Figure 5.6: **A**. Schematic overview of the generalization classification pattern analysis and the expected results from both hypotheses. **B**. The generalization classification results. SVM Generalization: the generalization accuracy of the classifier; 'Digit 1 as one dot': the correct classification performance of digit 1 as one dot. 'Confusion of digits as one dot': the confusion rate: how often is a digit other than '1' confused with one dot instead of the corresponding dot pattern sharing the same numerical magnitude. Error bars represent 95% confidence interval. The filled bullets indicate significant decoding ($p < 0.05$).

5.3.4 Generalization classification analyses

We subsequently ran generalization MVPA analyses by training a classifier to differentiate one dot from another dot condition (e.g. eight dots) and by subsequently testing this classifier on Arabic digit '1' and the Arabic digit sharing the same numerical magnitude as the other dot condition (e.g. digit '8') (Figure 5.6). The numerical cognition account predicts successful generalization because it postulates overlapping

neural representations for Arabic digits and dots that share the same numerical magnitude. In contrast, the object cognition account predicts a generalization at chance level and additionally expects the confusion of an Arabic digit of a large size (e.g. digit '8') with the one-dot condition, as these two conditions share the number of 'objects' on the screen.

The generalization accuracy from dots to Arabic Digits was not significant (all *ps* $>$ 0.26) in any of the 21 ROIs (Figure 5.6B showing most relevant ROIs). This suggests that there is no abstract coding of numerical magnitude that is independent of format, in contrast to what is expected from the numerical cognition account, This finding is consistent with previous reports that classifiers trained on multi-voxel patterns of one format tend to generalize very poorly (Eger et al., 2009) or even not at all towards stimuli with the same numerical magnitudes represented in a different format (Bulthé, De Smedt & Op de Beeck, 2014; Damarla & Just, 2012).

In addition to the absence of generalization, the object cognition account also predicts a confusion of each Arabic digit condition (e.g. digit '8') with the one-dot condition instead of a classification as the dot condition sharing the numerical magnitude with the Arabic digit (e.g. eight dots). This is what we observed (Figure 5.6B): all Arabic digits, independent of their numerical magnitude were more often classified as one dot instead of the dot pattern with the same numerical magnitude (e.g. two dots, four dots and eight dots). This effect was present in All Regions (t_{11} = 11.65, $p <$ 0.0001), Parietal Cortex (t_{11} = 6.48, $p <$ 0.0001), IPS (t_{11} = 5.58, p = 0.0002), left posterior IPS (t_{11} = 2.64, p = 0.02), right posterior IPS (t_{11} = 3.17, p = 0.01), right posterior IPS (t_{11} = 3.15, p = 0.01), except for left posterior IPS, where the same trend was present but not significant (t_{11} = 1.68, p = 0.12). For most of the other defined ROIs this confusion rate was significant, except for visual word form area, Wernicke, left inferior frontal gyrus and, left and right superior frontal gyrus, where the same trend was again present but not significant.

5.4 Discussion

The results from this study failed to support the hypothesis that the IPS contains abstract numerical magnitude neural representations. Instead, the results confirmed several predictions from the object cognition account. The linear regression on the decoding analyses showed a significant increase in the dissimilarity of neural patterns between Arabic digits and a dot pattern when more dots were being presented. This finding was further bolstered by the generalization MVPA where Arabic digits were significantly classified as one dot pattern instead of the dot pattern with the same numerical magnitude as the Arabic digit. These findings were observed in the IPS, parietal cortex and other regions of interest.

5.4.1 Absence of cross-format generalization

The abovementioned absence of a cross-format generalization from dots (e.g. four versus eight dots) to Arabic digits (e.g. Arabic digit 4 versus Arabic digit 8) suggests that there were no overlapping neural representations for Arabic digits and dots sharing the same numerical magnitude.

Although this is in line with previous reports by (Damarla & Just, 2012) and Bulthé, De Smedt & Op de Beeck (2014), it is important to point out that this is still a null result. However, in the present study, these null results cannot be explained by a lack of power or to task difficulty differences between both formats. First, the failed cross-format generalization was not due to a lack of power, because it resulted from a significant classification of digit '1' as one dot, and a significant and equally large confusion classification of other Arabic digits. Second, the null result of cross-format generalization did not seem to reflect possible task difficulty differences between the Arabic digits and dot comparison tasks, which in theory could modulate IPS and parietal activation in a way that is interfering with generalization across formats. The behavioral data of the number comparison task in our experiment showed no significant differences in accuracy and reaction times between both formats. So, neither a

lack of power in our data or differences in task difficulty of formats can explain the absence of cross-format generalization.

A similar analysis as our confusion generalization analysis was performed in the study of Eger et al. (2009), which is briefly mentioned in their supplemental data. Their results showed also a high confusion of Arabic digits with one dot, instead of being classified as the corresponding dot condition sharing the same numerical magnitude. These authors concluded that "This could potentially indicate that the classifier has access to a mixture of codes: one of them being a non-symbolic one (number of objects) and therefore the pattern for a digit (a single object) is most similar to the one for two dots." So, both our data as Eger et al. (2009) their data seem to converge with the object cognition account, namely numerical magnitudes processed as number of objects.

The cross-format generalization applied for the confusion analysis in our study was only observed in the direction from dots to Arabic digits. Eger et al. (2009) observed a significant generalization from Arabic digits to dots (but not vice versa). We tested the generalization from Arabic digits to dots in the current dataset and found no significant generalization from Arabic digits to dots in any of the ROIs ($ps > 0.30$). This failure to replicate the asymmetrical cross-format generalization of Eger et al. (2009) has also been reported in two recent studies (Bulthé, De Smedt & Op de Beeck, 2014; Damarla & Just, 2012).

The lack of cross-format generalization in the parietal cortex and IPS does not mean an absence of neural representations of Arabic digits or dots in those regions. The current study and previous studies (Bulthé, De Smedt & Op de Beeck, 2014; Damarla & Just, 2012; Eger et al., 2009) have clearly shown that it is possible to distinguish between different neural representations of Arabic digits and dots in parietal regions, which indicates that some numerical aspects of these stimuli are being processed in IPS and parietal cortex. However, the absence of cross-format generalization due to the confusion of Arabic digits as one dot in the current study suggests that these

representations are not overlapping.

5.4.2 Format-specific processing in other brain regions

Previous neuroimaging studies have pointed to other regions in the cortex that are important when processing Arabic digits and dots, such as temporo-parietal junction, fusiform gyrus, dorsal prefrontal cortex, angular gyrus, etc. (Ansari, 2007; Dehaene et al., 2003; Holloway et al., 2013; Lyons & Ansari, 2009; Menon et al., 2000; Piazza et al., 2007; Polk et al., 2001; Roggeman et al., 2011; Santens et al., 2010). To test the presence of neural representations of numerical magnitudes in regions outside the IPS and the parietal cortex, we included several extra-parietal ROIs (see Methods) in our analyses. Many ROIs showed significant within-format decoding for both Arabic digits and dots demonstrating distinct neural representations for both formats.

The significant decoding accuracies in regions outside the parietal cortex, demonstrate the presence of distinguishable neural representations for Arabic digits and dots in those regions. However, this does not mean these representations reflect an underlying 'numerical' magnitude, let alone an abstract numerical magnitude. This can be illustrated by the findings of All Regions ROI that was included in the present study. More specifically the All Regions ROI has stronger distinct neural representations of dots and Arabic digits than the parietal cortex or IPS. This does not mean that in all the regions of the human cortex Arabic digits and dots are processed in the same way or that the underlying neural representations are identical across regions. It only reflects the many processes that contribute to the emergence of symbolic and non-symbolic numerical magnitude representations. For example, occipital regions are known to represent the visual properties of stimuli and the prefrontal cortex might process task-related aspects (e.g. process small and large numbers differently).

In this context, it is not surprising that the decoding accuracies in All Regions (compared to parietal cortex and IPS) were much higher for dots than for Arabic digits because non-numerical features, such as visual characteristics, were much more present

in the dots. These visual characteristics probably emerged from the occipital lobe, because when this lobe is excluded from the All Regions ROI the decoding accuracies dropped to the level of the parietal cortex and IPS.

5.4.3 Other possible visual processes

It is important to point out that the object cognition account is only one of a group of related visually-based hypotheses one might evoke to explain our results. The dot pattern conditions, when averaged across all individual trials in each condition, differ from each other on multiple dimensions (other than the number of elements), such as the number of black pixels, clutter or complexity of the stimulus. All such visually based hypotheses of IPS-activity stand in sharp contrast with the idea of an abstract number module and thus serve an equivalent purpose in the context of the present study.

Based on the results of the current study, we might not be able to pinpoint which visual dimension is the most dominant to the extent that our stimulus set does not fully dissociates them. Although the individual trials vary a lot on these dimensions within conditions (see Methods), more so than the average across all items varies between conditions, there was nevertheless an average difference between conditions on several visual dimensions. For example, there were, first, some differences between the dot conditions in terms of the number of black pixels. The percentages of black pixels relative to the total number of pixels on the screen: 6.74% (one dot), 12.03 % (two dots), 12.21% (four dots), and 12.48% (eight dots). The percentages were lower for the symbols conditions (‘1’: 0.83%; ‘2’: 1.49%; ‘4’: 1.40%; ‘8’: 1.83%), and as such the number of black pixels could be an explanation for our observation that all the symbol conditions were more similar to one dot than to patterns with more dots. However, the percentages were highly similar for two, four, and eight dots, whereas the decoding accuracy between symbols and two-dot patterns was clearly lower than between symbols and eight-dot patterns (this effect is significant in all parietal ROIs, with all $ps < 0.044$). Thus, at a quantitative level, it

is unlikely that this particular visual hypothesis regarding the number of black pixels explains the current findings.

'Clutter' is another visual property which could partially explain our results. This property is very difficult to dissociate from the number of objects. The same applies to the complexity of the total display, although this might depend upon how 'complexity' is exactly defined and whether it takes into account the complexity of the individual objects (e.g., an Arabic digit is visually more complex than a dot). Even though we cannot precisely pinpoint the exact visual dimension that explains our results, we observed very similar results in all our ROIs, all the way down to primary visual cortex in Brodman area 17, which suggests that at least for some areas the explanation for our findings has to be found in relatively simple visual dimensions. Nevertheless, for parietal areas, the hypothesis in terms of the number of objects comes into the picture as a particularly likely candidate, because studies in the object cognition literature as a whole have controlled for quite a number of visual dimensions and have already revealed the importance of this visually based stimulus property for activation in areas around the IPS.

5.4.4 Reconciling the object cognition account with recent studies on numerical processing

The current results are consistent with the findings of two very recent fMRI studies performed at high field strength (7T). He et al. (2014) showed that the IPS activity did not differ between dots and Arabic digits when small numerical magnitudes (<4) were presented, but that with increasing numerical magnitude (>6), the differences between symbolic and non-symbolic formats became more prominent in the IPS. This result can also be expected by the object cognition account: when numerical magnitude increases, the dot patterns contain a larger number of visual units than the Arabic digits, thus IPS activity between the formats will become less similar because they do not contain the same number of visual units anymore.

Another 7T fMRI study (Harvey et al., 2013) showed a clear topographic representation of numerical magnitude in the human parietal cortex for dot patterns but not for Arabic digits. Based upon the object cognition account, one would expect that the Arabic digits (<10) are mapped onto the one dot area in the topographic representation of the number of visual elements and are seen as similar. In light of this account, the finding of Harvey et al. (2013) is not surprising since their study showed no significant differences in activation in parietal regions between the Arabic digits. Because most of them contained the same number of visual elements, namely one visual element, the parietal regions would not handle them differently according to the object cognition account.

5.5 Conclusion

By integrating two research domains and applying MVPA analyses, we were able to show that there are no overlapping activity patterns between Arabic digits and dots in the IPS and any of its subparts. In line with studies on object cognition, which reported that the IPS processes the number of objects presented (Song & Jiang, 2006; Todd & Marois, 2005; Vogel & Machizawa, 2004; Y. Xu, 2008; Y. Xu & Chun, 2007b), our data suggest that Arabic digits are more related to one dot than to dot patterns with corresponding numerical magnitude. This significant finding contradicts the hypothesis that numbers would be processed in a format-independent manner in the human parietal cortex.

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Part III

Neural markers of dyscalculia

6 Less precise non-symbolic number representations in dyscalculia

The contributions of the first author are:

- Literature study
- Development of the code for the classification algorithms of empirical data
- Development of the searchlight code for empirical data
- Development of the code for subject classification
- Co-collecting empirical data
- Perform all analyses
- Co-interpretation of empirical results
- Co-formulation of conclusions
- Text redacting

Under review as

Bulthé, J., Prinsen, J., Duyck, S., Daniels, N., Op de Beeck, H., & De Smedt, B. (2017). Less precise neural representations of number in dyscalculia.

Abstract

Developmental dyscalculia (DD) is a neurodevelopmental learning disorder with a severe and persistent impairment in mathematical ability. DD is hypothesized to originate from less precise number representations in the IPS, a possibility that has not been directly tested. We evaluated this hypothesis for the first time with multivoxel pattern analysis to fMRI data acquired during a number comparison task, which allowed us to directly investigate if the neural representations of number in 24 human adults with DD were more overlapping than those of 24 carefully matched controls. Our findings confirm at the neural level that adults with DD have less precise non-symbolic magnitude representations. This was observed in not only parietal but also in temporal and frontal regions. In sum, the severe and very specific behavioral deficits in mathematical ability in DD are related to less precise magnitude representations in multiple brain regions.

6

6.1 Introduction

Successfully acquiring basic mathematical skills is crucial in Western society as the quality of these skills predict income (Estrada-Mejia et al., 2016), socio-economic status (Ritchie & Bates, 2013), medical decision making (Reyna et al., 2009), and even mortgage default (Gerardi et al., 2013). However, 5 to 7% of the population has persistent mathematical difficulties despite normal intelligence, absence of neurological injuries, and adequate learning interventions (Butterworth et al., 2011). This learning disorder has been described as DD. Even though DD is as prevalent as dyslexia (Bishop, 2010) and autism spectrum disorder (Elsabbagh et al., 2012), it has been far less investigated in cognitive neuroscience despite its life-long consequences in schooling, everyday life, employment, and health management (Rubinsten & Henik, 2009).

DD is thought to originate from impaired numerical magnitude processing (Rubinsten & Henik, 2009; Butterworth et al., 2011; De Smedt et al., 2013). As the representation and manipulation of numerical quantity is thought to be a key function of the IPS (Dehaene et al., 2003), it has been suggested that the difficulties in numerical magnitude processing in DD originate from IPS abnormalities (Rubinsten & Henik, 2009).

However, previous neuroimaging studies examining the overall level of activity in the IPS in DD have revealed mixed results. Price et al. (2007) revealed decreased IPS activation in children with DD during non-symbolic number comparison. This hypoactivation in the IPS has been reported in other neuroimaging studies with other task requirements as well, such as symbolic number comparison and arithmetic problem solving (Mussolin et al., 2010; Ashkenazi et al., 2012). On the other hand, Rosenberg-Lee et al. (2015) more recently showed that children with DD showed increased activity in the IPS during arithmetic problem solving.

The literature becomes even more complicated when we consider that, depending on the nature and complexity of specific tasks, mathematical information processing also involves activation and deactivation of a more distributed network of regions such as the superior parietal lobule, fusiform gyri, supramarginal gyrus, and inferior and superior frontal regions (Menon et al., 2000; Zago et al., 2001; Wu et al., 2009; Grabner et al., 2013; Menon, 2014; Rosenberg-Lee et al., 2015) and therefore, studies that restrict their focus to abnormal IPS function in DD are severely biased.

One major shortcoming of all these studies is that they investigate number processing in a very indirect manner by only considering the overall activation level in cortical regions. To date, no study has investigated the neural quality of magnitude representations in DD. Such research is crucial because it allows us to empirically verify an often-made prediction that the neurobiological origin of this neurodevelopmental disorder is in the less precise neural representations for numerical magnitudes and consequently poorer number processing (Dehaene et al., 2003; Butterworth et al., 2011).

The quality of neural representations can be investigated via MVPA (Norman et al., 2006). These methods have gained in popularity the last decade because they allow to test if neural representations of stimuli are distinguishable in a certain ROI. Neuroimaging studies on numerical cognition in healthy individuals have succeeded to distinguish different neural representations of symbolic and non-symbolic numerosities in various brain regions that are not restricted to the IPS (Eger et al., 2009; Damarla & Just, 2012; Bulthé, De Smedt & Op de Beeck, 2014; Bulthé et al., 2015; Lyons et al., 2015). It remains to be determined whether these neural representations of non-symbolic and symbolic magnitudes are less precise in individuals with DD.

This neuroimaging study provides the first investigation of the quality of neural magnitude representations in DD. We applied a whole-brain searchlight analysis and ROI-based MVPA to search for those regions where a difference in precision of neural magnitude representations between the two groups could be observed. Our results show clearly impaired non-symbolic magnitude representations in DD in frontal cortex, parietal lobule, and IPS.

6.2 Materials & Methods

Participants

In total, 54 adult participants took part in this study as paid volunteers. Due to technical issues with the scanner, a useful dataset was only acquired for 48 participants (all females, aged between 18 and 27 (mean (M): 21.81; SD: 2.16), three left-handed participants with DD, and two left-handed participants in the control group), including 24 participants with DD and 24 control participants with normal achievement in mathematics. All participants had normal or corrected-to-normal vision and reported no neurological or psychiatric history. An interview with all the participants was conducted to confirm that all individuals with DD and none of the control participants met the DSM-V criteria for specific learning disorder in mathematics (DD). All par-

ticipants provided two written informed consents, one before the behavioral session and one prior to scanning. The study was approved by the medical ethics committee of KU Leuven.

Matching dyscalculia group and control group

All participants successfully completed secondary school and they were either in college or university. The two groups were individually matched pairwise for their education in secondary school and college/university, gender, and age (see Table 6.1). We evaluated their mathematical and reading skills, motor speed, and intelligence to ensure the groups were matched for all these measures, except for mathematics. Statistical analyses for all the behavioral measures were done in Matlab version 8.3.0.532 (R2014a).

First, differences in mathematical abilities were assessed by three tests. Tempo Test Calculation (De Vos, 1992) and French Kit (French et al., 1963) are two timed standardized paper-and-pencil tests for one- and multi-digit calculation, respectively, (addition, subtraction, multiplication, and division). Additionally, the arithmetic subtest of the WAIS (Wechsler Adult Intelligence Scale III), which involves a series of verbally presented word problems without time pressure, was administered for each participant.

Second, reading abilities were assessed by two standardized reading tests in which as many existing words (Brus, 1999) and pseudo-words (Van den Bos, 1999) had to be read as fast as possible in one minute. Both reading scores were averaged after transformation to Z-scores. These reading tests were done to verify the absence of comorbidity with dyslexia.

Third, measures of verbal and non-verbal intelligence were obtained by means of the Vocabulary and Matrix Reasoning subtests of the WAIS, respectively.

Table 6.1: Descriptive statistics on matching variables.

	Dyscalculia Group	**Control Group**	$\mathbf{t}_{46}$	***p***
Descriptive Information				
N	24	24	-	-
Age (in years)	21.96 (2.16)	21.67 (2.20)	0.46	0.65
Mathematical Abilities				
French Kit	35.00 (7.97)	54.50 (15.86)	5.38	<0.0001
Tempo Test Arithmetic	113 (17.46)	148.75 (21.92)	6.25	<0.0001
Arithmetic (WAIS)*	7.50 (2.06)	10.79 (2.21)	5.34	<0.0001
Reading				
Z-score Reading	-0.20 (1.12)	0.20 (0.62)	1.49	0.14
IQ Measures				
Nonverbal - Matrix reasoning (WAIS)*	9.08 (2.90)	10.23 (3.01)	1.32	0.19
Verbal - Vocabulary (WAIS)*	10.79 (2.99)	12.08 (2.26)	1.69	0.10
Motor Speed Task				
Accuracy (%)	96.88 (10.82)	98.75 (2.21)	0.83	0.41
Reaction times (ms)	399.4 (0.08)	362.4 (0.06)	-1.80	0.08

Standard deviations are shown in parentheses. * Standardized score with M = 10 and SD = 3.

Lastly, to ensure that any group differences in reaction time for the experimental task (number comparison) in the scanner were not due to group differences in processing speed, participants performed a motor speed task on a computer. During this task subjects had to decide, in a quick but accurate manner, on which side the stimulus with a white surface was presented, by pressing the corresponding key (De Smedt et al., 2010).

fMRI Acquisition

Stimuli

The stimuli in this experiment were the same as a previous study (Bulthé, De Smedt & Op de Beeck, 2014). Stimuli in the experimental runs consisted of the numerical magnitudes 2, 4, 6 or 8, either displayed as symbolic numbers (Arabic digits) or non-symbolic numbers (a collection of white dots on a black background). We controlled the non-symbolic stimuli for intensive (individual item size and inter-item spacing) and extensive (total luminance and total area spanned by the non-symbolic numbers) confounding parameters by varying them randomly across the dot displays (Dehaene et al., 2005). Adaptation of the symbolic numbers was minimized by varying the position and size across trials.

Stimuli were presented via Psychtoolbox 3 (Brainard, 1997) and via a NEC projector projected onto a screen located approximately 46 cm from participants' eyes.

Design

The experimental runs had a short-block design with variable block duration, which was the same design as in Bulthé, De Smedt & Op de Beeck (2014). Short blocks (4, 5 or 6s) were used to prevent loss of attention and to minimize potential adaptation effects during one condition. A fixation block of 8s was presented at the beginning and end of the run. During the duration of one experimental block the same numerosity in the same format was repeated in sequences of 4, 5 or 6 trials. During the experimental runs, participants had to perform a number comparison task (indicate smaller or larger than five) every time the numerosity and/or format (non-symbolic versus symbolic) changed, which made the participants explicitly access numerical magnitude representations Piazza et al. (2004b). Per participant, between 8 and 12 experimental runs were acquired.

Statistical analyses for the behavioral measures (accuracy and reaction time) of the number comparison task in the scanner were done in Matlab version 8.3.0.532 (R2014a). The localizer runs consisted of the same design as Bulthé, De Smedt & Op de Beeck (2014); Bulthé et al. (2015). Participants had to subtract two numbers ranging from 1 to 20 from each other and needed to indicate if the solution was even or odd. Two localizer runs were obtained per participant.

fMRI Data Acquisition

fMRI data was acquired in a 3T Philips Ingenia CX Scanner with a 32-channel head coil using a T2*-weighted EPI pulse sequence (50 slices, 2.10 $\times$ 2.15 mm in plane acquisition voxel size, slice thickness 2 mm, interslice gap 0.2 mm, TR = 3000 ms, TE = 30 ms, flip angle = 90, 100 $\times$ 97 acquisition matrix). For each participant also

a T1-weighted anatomical volume was obtained (182 slices, resolution 0.98 $\times$ 0.98 $\times$ 1.2 mm, TR = 9.6 ms, TE = 4.6 ms, 256 $\times$ 256 acquisition matrix).

fMRI Analyses

fMRI Preprocessing

The data were processed using the Statistical Parametric Mapping software (SPM 12, Wellcome Department of Cognitive Neurology, London) in Matlab. Anatomical images were normalized to the standard brain template defined by the Montreal Neurological 152-brains average. Functional images were corrected for slice timing differences. Realignment between images to correct for motion across and within sessions was done, resulting in a set of motion parameters that were used as confounds when modelling the general linear model. No runs for any of the participants had to be excluded for extensive motion (based on a criterion of movement in any direction for more than one voxel size). Co-registration of the functional data and the anatomical image was performed. During normalization functional images were resampled to a voxel size of 2 $\times$ 2 $\times$ 2 mm. Functional images were spatially smoothed to suppress high-frequency noise by convolving them with a Gaussian kernel of 4 mm FWHM for subsequent multivariate voxel pattern analyses and 8 mm FWHM for subsequent second-level univariate analyses.

Statistical Analysis

For each voxel the experimental effect in a block was estimated by applying a general linear model. This resulted in beta-values for each condition (including the fixation condition) and six motion parameters per run. *T*-statistics (resulting from conditions vs. baseline) were calculated and used as input for subsequent multivariate analysis as *t*-statistics, taking both the mean and the variance of the activations into account (Misaki et al., 2010). For IPS the analyses were repeated using the beta values, resulting in very similar effects.

Regions of Interest

The four lobes (occipital, temporal, parietal, and frontal) ROIs were made with an anatomical mask in the WFU PickAtlas Toolbox (Wake Forrest University PickAtlas, `fmri.wfubmc.edu/cms/software`), we selected the voxels based on the conjunction of the voxels in that mask that survived the functional contrast (task minus fixation) from the independent localizer scans at an uncorrected threshold at $p < 0.001$.

For the IPS and its subparts there was no anatomical mask available, so we delineated these ROIs manually on the functional contrast of the localizer scans (uncorrected threshold at $p < 0.01$). All ROIs were created at individual level.

Univariate Analysis

For every participant two contrasts for the experimental runs were estimated: symbolic numbers minus fixation and non-symbolic numbers minus fixation. For this analysis, no distinction was made between the different numerical magnitudes within each format. A second-level group analysis in SPM12 was done for these contrasts to test for activation differences for symbolic numbers and non-symbolic numbers between the two groups on a whole brain level (threshold of $p < 0.05$ after FWE correction at voxel-wise level). Figures for this analysis were made with BrainNet Viewer (Xia et al., 2013).

A ROI-based univariate analysis was also conducted to test for group differences within each format. We performed two-sample *t*-tests and corrected for multiple comparisons with FDR for the four lobes and for the IPS subparts separately.

Multivariate Analysis

Subject classification based upon spatial variation in univariate activity levels Instead of decoding different conditions within one subject, it is possible to decode between the functional data of participants from the control group and the DD group. In other words, can we differentiate based on functional activity between the two

groups? For this analysis, we used the functional contrasts 'symbolic numbers minus fixation' and 'non-symbolic numbers minus fixation' from the experimental runs for every participant. It is important to point out that this analysis does not tackle the underlying differences in the quality of the neural representations of symbolic numbers and non-symbolic numbers between the groups, but tests if there is a more general difference in activation between the two groups when symbolic and non-symbolic numbers are processed. In this way, this analysis is more closely related to a second level univariate analysis than to multivariate ROI-based decoding and searchlight analysis. The main difference with a second level univariate analysis lies in the fact that there is no activity-based comparison at the level of single voxels, but a spatial pattern comparison between the two groups across the whole brain or across a selected ROI.

The classification was performed with linear SVM with the following parameters: a radial basis function kernel as decision function with parameter gamma set to 1; a C-SVC classification algorithm was used with parameter C set to 1. We applied a Leave-one-pair-out-cross-validation (LPOCV) technique, similar to the one used in Ung et al. (2014). With this method the classifier was trained on all participants, except for one random participant from the control group and one random participant from the DD group. Afterwards, the trained model was tested on this left-out pair. This procedure was repeated until each participant was once left out. Because of this random division into pairs, slightly different accuracies can occur depending on the division. For this, the LPOCV was run 1000 times, and the results were averaged across all these repeats.

Statistics were obtained by a Monte Carlo Permutation test (Mourão-Miranda et al., 2005). The class labels of the training set were 1000 times randomly permuted and the same LPOCV procedure as described above was applied. A *p*-value for the subject classification accuracy was obtained by the number of times the permutation accuracy is greater than or equal to the subject classification accuracy, divided by 1000. For this subject classification, we noted that the permutation-based threshold for stat-

istical significance was actually very similar to the threshold as it would be set by a simple parametric binomial test taking into account the proportion of participants classified in a particular group. To correct for multiple comparisons, we applied a FDR-correction across the four lobes and across the IPS regions.

Whole brain searchlight analysis of decoding of neural magnitude representations The method is particularly suited for finding where in the brain the local spatial activity pattern differs across conditions without selecting any ROIs (Kriegeskorte et al., 2006; Kriegeskorte & Bandettini, 2007).

For the searchlight analysis, we used "The Decoding Toolbox" together with own custom made code in Matlab (Hebart et al., 2015). The classification model (SVM) and its parameters for the ROI-based decoding were similar to the ones used for the subject classification analysis.

During the searchlight analysis a sphere with a radius of two voxels (volume of max. 33 voxels) was sequentially moved across the entire grey-matter volume (similar as Bulthé, De Smedt & Op de Beeck (2014)). The searchlight analysis resulted in a map for each format per participant. Afterwards, the maps were spatially smoothed using Gaussian kernels of 8 mm FWHM (equal to the univariate smoothing level). Finally, a second-level analysis was done in SPM12 to test for group differences for both formats (threshold of $p < 0.05$ after FWE correction).

ROI-based decoding of neural magnitude representations For each ROI a decoding classification analysis was implemented with custom code written in Matlab (The MathWorks, Natrick, MA) using the LIBSVM toolbox (Chang & Lin, 2011). The classification model (SVM) and its parameters for the ROI-based decoding were similar to the ones used for the subject classification and searchlight analyses.

Response patterns for every condition in each run were extracted for each ROI, with in each pattern the *t*-values of all voxels in the ROI. The patterns were standardized

by subtracting the mean across voxels and then dividing this by the standard deviation across voxels for each condition. We followed a repeated random subsampling cross-validation procedure: The data were randomly divided into 70% training data and 30% test data (the latter were averaged to one response pattern per condition), and this was repeated 100 times.

The decoding accuracies were then averaged over two comparisons of interest: symbolic numbers (mean within-format decoding accuracy for symbolic numbers) and non-symbolic numbers (mean within-format decoding accuracy for non-symbolic numbers). Group differences were tested with a two-sample *t*-test and corrected for multiple comparisons with FDR for the four lobes and for the IPS subparts separately.

6.3 Results

Behavioral and neuroimaging data were collected in 24 college/university students with and 24 college/university students without DD. All adults with DD met the DSM-V (American Psychiatric Association, 2013) criteria for specific learning disorder. Both groups were matched on sex, intelligence, age, educational history and reading ability. They differed significantly, as expected, in their mathematical abilities (Table 6.1).

6.3.1 Behavioral Analysis

A 2 $\times$ 2 ANOVA (group $\times$ format) was performed to test for group and format differences on the number comparison task during the experimental runs. For accuracy there was no significant group difference between the control group (95.75%) and DD group (94.77%) ($F_{1,92} = 2.29$, $p = 0.13$). A significant effect for format was observed and accuracy was higher for symbolic numbers than for non-symbolic numbers ($F_{1,92} = 41.04$, $p < 0.001$): 97.35% and 93.17%, respectively. There was no significant interaction effect between group and format ($F_{1,92} = 0.01$, $p = 0.92$).

For reaction time, a significant group difference was observed with faster response times for controls (0.90s) than for individuals with DD (1.18s) ($F_{1,92} = 41.2$, $p < 0.001$). Again, a significant format effect was present with faster reaction times for symbolic numbers (0.91s) than for non-symbolic numbers (1.17s) ($F_{1,92} = 34.67$, $p < 0.001$). There was no interaction between group and format ($F_{1,92} = 0.36$, $p = 0.55$).

Thus, overall, the two subject groups performed the task equally well, but individuals with DD were significantly slower compared to the control group.

6.3.2 Neural activation levels for symbolic and non-symbolic numbers

Univariate Analyses

In a first step, in line with earlier studies, we performed univariate analyses to test for group differences in overall activation level. No significant group differences for symbolic and non-symbolic numbers were found on a whole brain voxel-wise *t*-test (second-level analysis, voxel-wise FWE corrected at $p < 0.05$). This is, on average, consistent with earlier observed task-dependent hyper- and hypo-activations in DD.

We also conducted an ROI-based univariate analysis to test the average activation differences between the two groups within a ROI for each format. For neither of the formats a significant group effect was found in any of the ROIs that were defined a priori: occipital cortex (symbolic: $t_{46} = 1.70$, $p_{\text{FDR}} = 0.13$; non-symbolic: $t_{46} = 1.44$, $p_{\text{FDR}} = 0.21$), parietal cortex (symbolic: $t_{46} = 2.03$, $p_{\text{FDR}} = 0.10$; non-symbolic: $t_{46} = 1.71$, $p_{\text{FDR}} = 0.19$), temporal cortex (symbolic: $t_{46} = 2.08$, $p_{\text{FDR}} = 0.10$; non-symbolic: $t_{46} = 1.79$, $p_{\text{FDR}} = 0.19$), frontal cortex (symbolic: $t_{46} = 0.76$, $p_{\text{FDR}} = 0.45$; non-symbolic: $t_{46} = 1.07$, $p_{\text{FDR}} = 0.29$), IPS (symbolic: $t_{46} = 1.74$, $p_{\text{FDR}} = 0.14$; non-symbolic: $t_{46} = 1.46$, $p_{\text{FDR}} = 0.21$), left anterior IPS (symbolic: $t_{46} = 1.34$, $p_{\text{FDR}} = 0.20$; non-symbolic: $t_{46} = 1.07$, $p_{\text{FDR}} = 0.29$), right anterior IPS (symbolic: $t_{46} = 1.72$, $p_{\text{FDR}} = 0.19$; non-symbolic: $t_{46} = 1.87$, $p_{\text{FDR}} = 0.22$), left posterior IPS

(symbolic: $t_{46} = 1.29$, $p_{\text{FDR}} = 0.20$; non-symbolic: $t_{46} = 1.08$, $p_{\text{FDR}} = 0.29$), and right posterior IPS (symbolic: $t_{46} = 2.08$, $p_{\text{FDR}} = 0.17$; non-symbolic: $t_{46} = 1.62$, $p_{\text{FDR}} = 0.22$).

Subject classification

To further investigate whether there were distinguishable patterns of activation versus fixation between the two groups with as sensitive methods as possible, we applied a subject classification procedure in which the univariate activation levels are combined across voxels. Subject classification allowed us to examine if the activation patterns of both groups for either formats at various spatial levels were different enough to be picked up by a classifier.

The results of the subject classification analysis did not show a significant subject classification accuracy in any of the ROIs for symbolic ($0.38 <$ classification accuracy < 0.59, $0.68 < p_{\text{FDR}} < 0.99$) or non-symbolic numbers ($0.33 <$ classification accuracy < 0.64, $0.17 < p_{\text{FDR}} < 0.99$).

Thus, even with sensitive classification methods we did not find significant differences between subject groups in terms of the general pattern of activation. These analyses suggest that the same representations and processes seemed to be involved in the two groups.

6.3.3 Quality of neural representations of symbolic and non-symbolic numbers

Searchlight Analysis

The above described results showed no significant group differences in level of activation for either formats. All these analyses are based upon the level of activation versus fixation. Earlier studies also focused upon such activation levels. Here we proceed with more refined analyses which allow to assess the quality of neural rep-

resentations. Therefore, we applied a whole-brain MVPA searchlight analysis based upon the decoding of different magnitudes. This analysis was performed separately for the two formats, non-symbolic and symbolic magnitude representations.

The searchlight analysis demonstrated specific 'hotspots' in both groups for non-symbolic and symbolic numbers representations (Figure 6.1, first two rows). For control participants the non-symbolic representations of different numerosities (e.g., 4 dots versus 8 dots) were distinguishable in many regions of the dorsal stream. In individuals with DD, the non-symbolic number representations were distinct in the occipital pole and a few patches in the parietal cortex (mainly superior parietal lobule).

An explicit comparison between groups for non-symbolic numbers (Figure 6.1) clearly demonstrated significantly less distinct non-symbolic number representations in the anterior parietal, frontal lobe, and a small spot in the temporal lobe for individuals with DD compared to controls.

For symbolic numbers we found much less regions with distinct number representations for both groups compared to non-symbolic numbers. This is consistent with earlier studies using a similar paradigm and data-analytic methods (Eger et al., 2009; Damarla & Just, 2012; Bulthé, De Smedt & Op de Beeck, 2014) which also showed a much lower ability to decode symbolic numbers compared to non-symbolic numbers. The searchlight maps of both groups were not significantly different for symbolic numbers, and thus it seems that for symbolic numbers there is no difference in how overlapping the neural representations are between both groups.

In both groups the classifier was also able to distinguish between symbolic numbers in the occipital pole and motor and somatosensory cortex. The significant accuracy in the motor and somatosensory cortex might be due to a response confound. Most (four out of six) pairwise comparisons of numbers are between conditions triggering different motor responses (e.g. smaller or larger than 5) and this might be picked

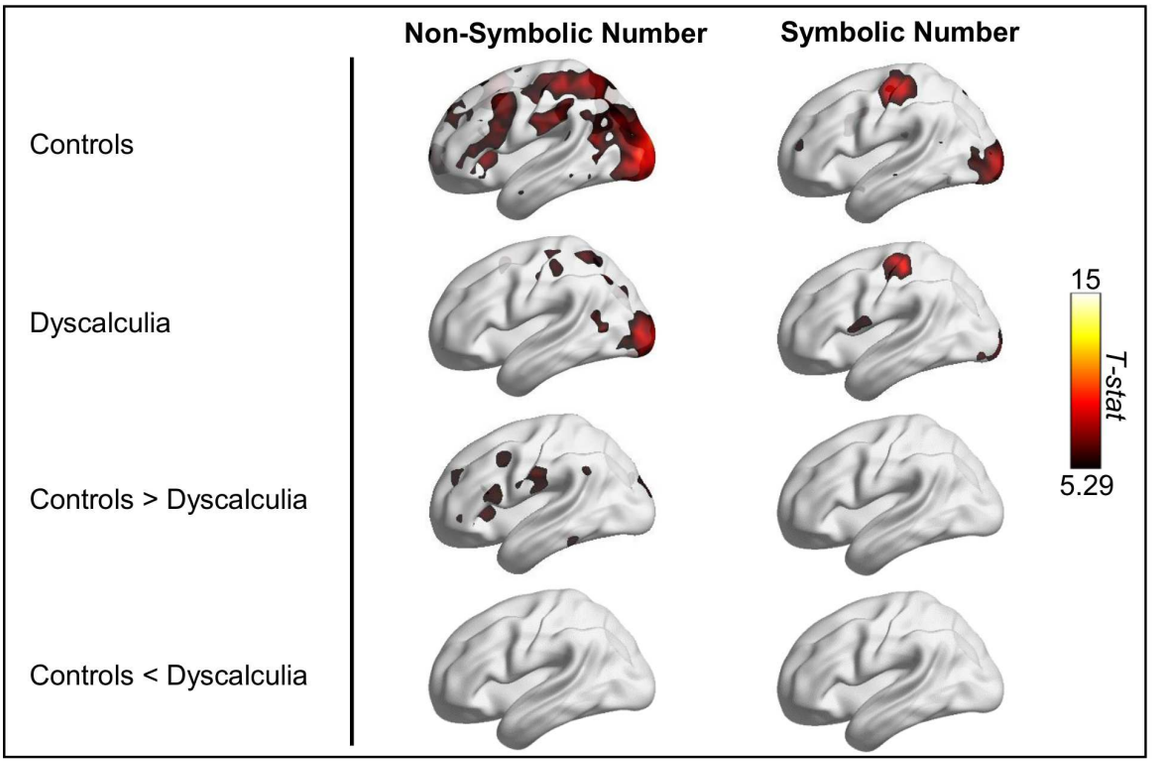

Figure 6.1: Searchlight results. Illustration of the decoding accuracies elicited by non-symbolic and symbolic numbers in the control group and the DD group. The difference in decoding accuracies between the two groups for each format is also illustrated. The results were corrected with FWE ($p < 0.05$).

up by the classifier. Note that in a different study with the same paradigm and only sixteen subjects we did not observe this effect (Bulthé, De Smedt & Op de Beeck, 2014), suggesting a small effect that can only be picked up by the classifier with enough data. These regions did not show any group difference.

ROI-based decoding

Importantly, the searchlight results should not be interpreted as evidence that number representations are relatively focal, because searchlight analyses are notoriously biased towards finding focal representations (Bulthé, van den Hurk et al., 2014). Therefore, we also applied ROI-based decoding analyses to look for more widespread differences between the two groups, first within the four lobes and then in the IPS and subparts (Figure 6.2).

Lobes The decoding accuracies for non-symbolic numbers were significantly different from chance level for both groups in all lobes (Figure 6.2A): occipital (controls: $t_{23} = 21.22$, $p_{\text{FDR}} < 0.001$; DD: $t_{23} = 14.52$, $p_{\text{FDR}} < 0.001$), parietal (controls: $t_{23} = 19.66$, $p_{\text{FDR}} < 0.001$; DD: $t_{23} = 14.61$, $p_{\text{FDR}} < 0.001$), temporal (controls: $t_{23} = 15.55$, $p_{\text{FDR}} < 0.001$; DD: $t_{23} = 10.75$, $p_{\text{FDR}} < 0.001$), and frontal (controls: $t_{23} = 16.10$, $p_{\text{FDR}} < 0.001$; DD: $t_{23} = 10.94$, $p_{\text{FDR}} < 0.001$). There was no significant group difference in the occipital lobe ($t_{46} = 1.63$, $p_{\text{FDR}} = 0.11$). A significant group difference was observed in the parietal lobe ($t_{46} = 2.49$, $p_{\text{FDR}} = 0.03$), temporal lobe ($t_{46} = 2.38$, $p_{\text{FDR}} = 0.03$), and frontal lobe ($t_{46} = 2.93$, $p_{\text{FDR}} = 0.02$), with more distinguishable neural patterns for non-symbolic numbers in controls than in DD.

The decoding accuracies for symbolic numbers (Figure 6.2B) were significantly different from chance level for both groups in occipital (controls: $t_{23} = 6.81$, $p_{\text{FDR}} < 0.001$; DD: $t_{23} = 4.88$, $p_{\text{FDR}} < 0.001$) and parietal (controls: $t_{23} = 3.07$, $p_{\text{FDR}} = 0.01$; DD: $t_{23} = 3.67$, $p_{\text{FDR}} = 0.001$) lobe. In the frontal cortex the classifier did not reach significance level for controls (controls: $t_{23} = 0.10$, $p_{\text{FDR}} = 0.92$), however in individuals with DD it was able to distinguish between different symbolic numbers (DD: $t_{23} = 2.57$, $p_{\text{FDR}} = 0.02$). There was no significant group difference in the occipital ($t_{46} = 1.63$, $p_{\text{FDR}} = 0.11$), parietal ($t_{46} = 2.49$, $p_{\text{FDR}} = 0.03$), temporal ($t_{46} = 2.49$, $p_{\text{FDR}} = 0.03$), and frontal ($t_{46} = 2.49$, $p_{\text{FDR}} = 0.03$) lobe for symbolic numbers.

Overall, these findings from ROI analyses confirm the searchlight results: For non-symbolic number representations, we found less distinct representations for individuals with DD in the parietal, temporal and frontal cortex. There were no significant group differences in the neural quality of symbolic number representations, although these representations were distinct for both groups in the occipital and parietal cortex.

IPS The neural patterns for non-symbolic numbers were distinct from each other in both groups in the IPS (Figure 6.2C) (controls: $t_{23} = 13.91$, $p < 0.001$; DD: $t_{23} = 10.05$, $p < 0.001$), left anterior IPS (controls: $t_{23} = 6.22$, $p_{\text{FDR}} < 0.001$; DD: $t_{23} =$

5.72, $p_{FDR} < 0.001$), right anterior IPS (controls: $t_{22} = 10.86$, $p_{FDR} < 0.001$; DD: $t_{22} = 6.37$, $p_{FDR} < 0.001$), left posterior IPS (controls: $t_{23} = 8.71$, $p_{FDR} < 0.001$; DD: $t_{23} = 6.09$, $p_{FDR} < 0.001$), and right posterior IPS (controls: $t_{23} = 9.02$, $p_{FDR} < 0.001$; DD: $t_{23} = 7.49$, $p_{FDR} < 0.001$). However, only in the IPS ($t_{46} = 2.50$, $p_{FDR} = 0.048$) and right anterior IPS ($t_{44} = 2.91$, $p_{FDR} = 0.02$) the distinctiveness of the non-symbolic number representations was significantly higher for controls than for DD. This effect was not present in the searchlight analysis, suggesting that the group difference in quality of non-symbolic number representations is not a local (e.g. in neighboring voxels) in the IPS or right anterior IPS.

The symbolic number representations were not significantly distinct for either group in the IPS and subparts: IPS (controls: $t_{23} = 1.43$, $p = 0.83$; DD: $t_{23} = 1.93$, $p = 0.07$), left anterior IPS (controls: $t_{23} = -.40$, $p_{FDR} = 0.39$; DD: $t_{23} = 1.77$, $p_{FDR} = 0.09$), right anterior IPS (controls: $t_{22} = 0.34$, $p_{FDR} = 0.17$; DD: $t_{22} = 0.56$, $p_{FDR} = 0.58$), left posterior IPS (controls: $t_{23} = -1.67$, $p_{FDR} = 0.12$; DD: $t_{23} = 1.64$, $p_{FDR} = 0.11$), and right posterior IPS (controls: $t_{23} = 1.84$, $p_{FDR} = 0.12$; DD: $t_{23} = -0.56$, $p_{FDR} = 0.58$). Hence, there were no group differences in the IPS or subparts, again confirming the searchlight analysis.

6.4 Discussion

This study is the first neuroimaging study on DD that directly tests if neural representations of numerical magnitude are more overlapping in adults with DD compared to adults without DD. We applied whole-brain and ROI-based multivariate analyses that clearly demonstrated less precise non-symbolic neural number representations in adults with DD throughout the dorsal stream, including the IPS.

We demonstrated this impaired quality of non-symbolic magnitude representations while participants were performing a numerical magnitude comparison task. We deliberately opted for timing parameters which allowed the participants with DD to perform the task quite well. In fact, their overall performance was not significantly

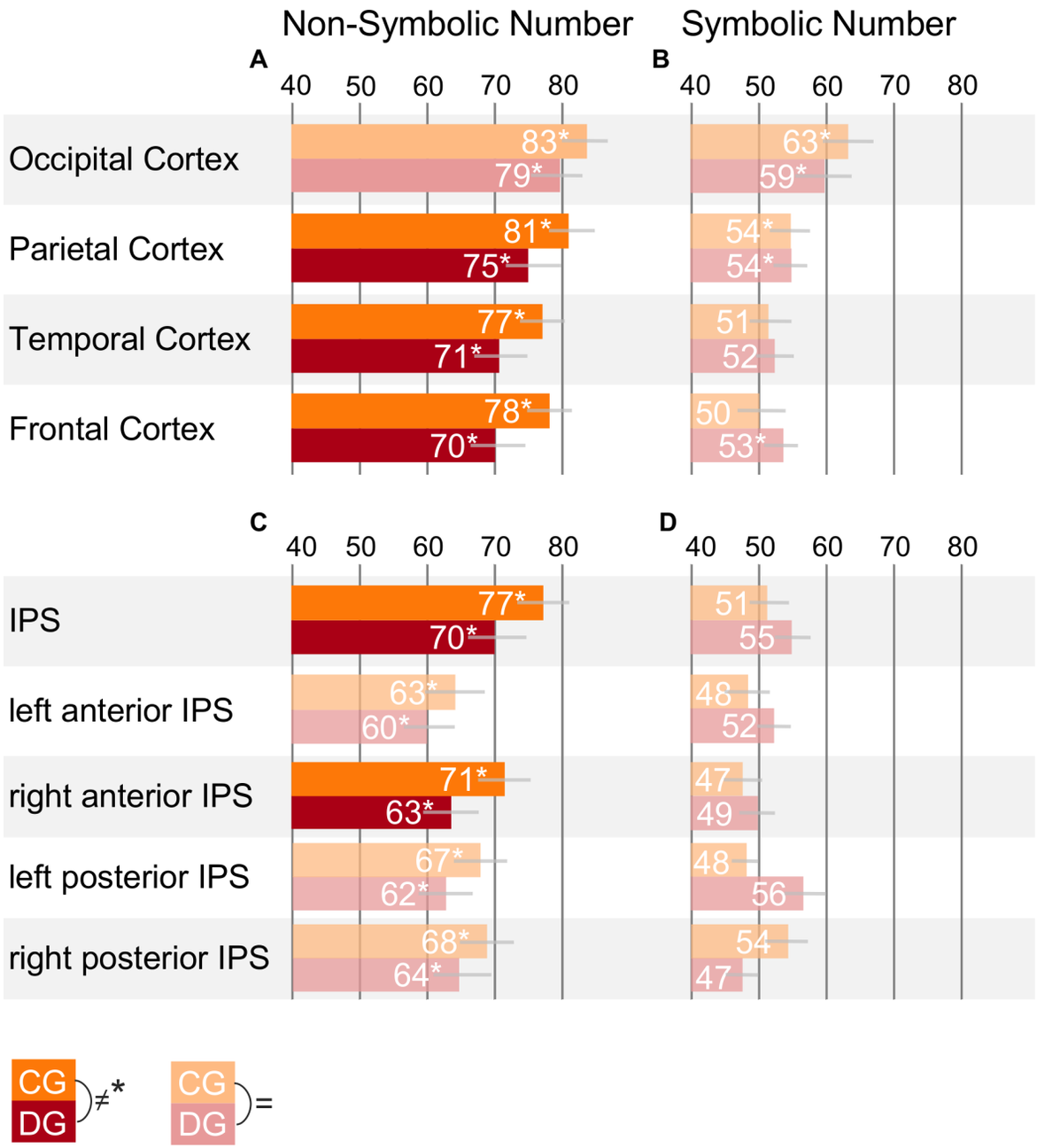

Figure 6.2: Decoding accuracies of controls and DD for non-symbolic and symbolic numbers for every ROI. Orange represents the control group (CG) and red the group with DD (DG). The asterisks represent a significant decoding accuracy for that group in that ROI. The dark colored bars represent a significant group difference between controls (orange) and DD (red). The dimmed bars represent a non-significant group effect. Error bars represent the 95% confidence interval for the decoding accuracy for that group in that ROI.

different from controls, they only required more time (slower reaction time). Because overall performance was the same, the impaired quality of magnitude representations at the neural level cannot be explained by one group not being able to perform the task and hence being less motivated/attentive. If anything, the slower reaction time of the participants with DD suggests that these subjects were processing the stimuli for a longer time, which could have resulted in a better quality of the magnitude representations. Overall, the behavioral task performance avoids that we have to take into account a performance discrepancy when interpreting the neural data. Strikingly, a previous study of phonological processing in dyslexia also compared subject groups with the same accuracy and a different reaction time (slower in the dyslexic group), and in that case found no difference in the quality of neural representations (Boets et al., 2013).

We demonstrated that the deficits in the quality of neural magnitude representations are spread out throughout the cortex, as was already suggested by a few studies of univariate levels of activation (Kaufmann et al., 2011; Rosenberg-Lee et al., 2015). In our study, the representations in these regions outside the parietal cortex might be related to numerical representations as well as to how these representations are recruited during more general processes. For example, frontal regions often play an important role in attention and working memory processes required for problem solving, also in numerical context.

This observation fits quite well with the increasing awareness that the neural origins of DD are may not be restricted to domain-specific deficits, such as impaired neural magnitude representations in typical numerical cognition regions (e.g. IPS or parietal regions) (Menon, 2011; Fias et al., 2013). Instead, its neural correlates might also include domain-general deficits and involve impairments that are not specific to math (Rubinsten & Henik, 2009; Fias et al., 2013; Wilson et al., 2015). For example, impairments in executive functions, working memory, attention or inhibitory control have been highlighted as potential risk factors for learning disorders and their comorbidity (Rubinsten & Henik, 2009; Vanbinst & De Smedt, 2016).

While the deficit in non-symbolic number processing for DD was very clear in our study, we found no group differences in the quality of magnitude representations for symbolic numbers. This does not necessarily mean that symbolic representations are not impaired in DD. Previous MVPA studies in healthy participants already showed that these symbolic representations are harder to detect than representations of non-symbolic magnitudes (Eger et al., 2009; Damarla & Just, 2012; Bulthé, De Smedt & Op de Beeck, 2014; Bulthé et al., 2015; Lyons et al., 2015). This was confirmed in the current study as we observed smaller decoding accuracies, also in controls, for symbolic magnitudes. Given that decoding performance was markedly lower for symbolic than for non-symbolic numbers, the lack of a significant group difference for symbolic numbers might arise from a lack of sensitivity to detect a possible underlying group difference. Future studies that investigate the quality of symbolic number representations in DD might consider to collect more scanning data of only symbolic numbers, increase the difficulty of the task, or use larger symbolic numbers to overcome this lack of sensitivity.

Our study is the first study to demonstrate that the quality of non-symbolic magnitude representations is affected in adults with DD. Although there have been previous studies on DD, they are very different from ours because of two major differences.

First, previous neuroimaging studies used univariate fMRI analyses that answer the question if there are altered levels of brain activation in individuals with DD. When we applied the same type of univariate analyses to our dataset, we failed to detect any clusters of voxels in the whole brain that showed a different level of activation in individuals with DD. It is not clear whether and in what direction our null results would deviate from earlier observed task-dependent altered levels of activations in DD as mixed results have been reported. Several studies have reported a decreased activation in DD during non-symbolic number comparison tasks (Price et al., 2007), arithmetic problem solving (Ashkenazi et al., 2012), and symbolic number comparison (Mussolin et al., 2010). On the other hand, others have reported increased

activity in the IPS during arithmetic problem solving in children with DD compared to matched controls (Rosenberg-Lee et al., 2015). Combining these previously found hyper- and hypoactivation in the IPS together, one could expect a null result, as we find.

Second, all previous functional neuroimaging work on DD has been carried out with children. Our study is the first functional neuroimaging study with adults diagnosed with DD. Hence, it was not known to date whether this functional altered activation levels in the IPS and other brain regions correlated with DD remain throughout the lifespan of persons with DD. Our results suggest that such differences in overall activity may have diminished during adulthood. This does not exclude the possibility that during development there might have been time points in development during which hyper- or hypoactivation in the IPS in children with DD is observed. On the other hand, it might be that such differences in overall activity only emerge when more complex numerical tasks (e.g. calculation instead of comparison) are used.

6.5 Conclusion

To conclude, our multivariate analyses results provided the first evidence that non-symbolic number representations were less precise in adults with DD in comparison to a strictly matched control group. These less precise non-symbolic number representations in DD were observed throughout the dorsal stream and the IPS, and were thus very widespread in the cortex. However, for symbolic magnitudes we did not observe any differences in neural quality between the two groups and further investigation is needed to unravel if symbolic neural representations are less precise in DD or not.

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6

7 Altered grey matter volume and functional connectivity in dyscalculia

The contributions of the first author are:

- Literature study
- Co-collecting empirical data
- Co-perform DTI analyses
- Perform fcMRI analyses and VBM analysis
- Co-interpretation of empirical results
- Co-formulation of conclusions
- Text redacting

Final stage before submission

Bulthé, J., Vanderauwera, J.*, Gillebert, CP., Dante, M., Op de Beeck, H., & De Smedt, B. (2017). Neuroanatomical correlates of dyscalculia in adults: a morphometry and connectivity neuroimaging study.*

Abstract

The underlying neural mechanisms of DD are still poorly understood. The handful of previous neuroimaging studies in DD demonstrated altered activity in a wide range of regions. In addition, it is important to look into how the connectivity, both structural and functional, is altered in individuals with DD. Surprisingly, there has been not a single neuroimaging study investigating if connectivity in adults with DD are altered. We used DTI, fcMRI and structural MRI to examine the neuroanatomical correlates of DD in adults, compared to a control group, strictly matched on age, gender, intelligence, education level, and reading abilities. We observed no differences in white matter connectivity in adults with DD. fcMRI showed hyperconnectivity between occipito-temporal regions in DD, which might reflect compensation mechanisms. Voxel-based morphometry revealed increased grey matter in the posterior cingulate cortex of adults with DD. Thus, by combining multiple neuroanatomical techniques, we demonstrated both functional connectivity impairments in occipito-temporal regions and increased grey matter in posterior cingulate cortex in adults with DD. Our findings are consistent with theoretical proposals that most neurodevelopmental disorders arise from a combination of diffuse functional disruptions, deficits in connectivity between regions, and anatomical differences.

7.1 Introduction

Developmental DD is a learning disorder affecting numerical and arithmetic skills, despite normal intelligence, and has a prevalence of 5-7% (Butterworth, 2010; Rubinsten & Henik, 2009). Although DD is as prevalent as dyslexia and autism, DD and related numerical disabilities have received much less attention in neuroscience research (Butterworth et al., 2011).

A wide variety of research has determined cortical regions involved in numerical and arithmetical processing in children and adults without DD (Ansari, 2008; Dehaene et al., 2003; Kucian & von Aster, 2015). Functional and structural neuroimaging studies have found that the IPS, the dorsal visual stream encompassing the superior parietal lobule, the angular and supramarginal gyri in posterior parietal cortex, and the ventral visual stream encompassing lingual and fusiform gyri are involved in numerical and arithmetic processing (Ansari, 2008; Ashkenazi et al., 2012; Menon et al., 2000; Piazza et al., 2007; Eger, 2016; Menon, 2015).

Abnormal function in these cortical regions has been related previously to specific learning disabilities in mathematics (Kucian et al., 2011; Mussolin et al., 2010; Price et al., 2007). However, most of studies published to date have been mainly focused on brain function, and very little is known about the connectivity and anatomical deficits linked to DD.

One approach to understand the possible impairments in these numerical and arithmetic processing networks related to mathematical disabilities, is to examine the white matter and functional connectivity of individuals with impaired mathematical skills (for review, see Matejko & Ansari (2014)). Impairments in mathematical skills have been previously related to parietal regions (Lebel et al., 2010), temporal sulcus (Molko et al., 2004), IPS (Molko et al., 2004; Barnea-Goraly et al., 2005), cerebellum (Lebel et al., 2010), and corpus callosum (Lebel et al., 2010; Van Beek et al., 2015).

Important to note, is that above discussed studies have been on specific disorders where mathematical disabilities are correlated to (e.g., Turner syndrome, velocardiofacial syndrom, traumatic brain injury, and fetal alcohol spectrum disorder). It is challenging to interpret these studies examining brain-behavior correlations in atypically developing participants since any associations between brain microstructure and mathematical skills could be specific to the disorder or a byproduct of the neuropathology. Consequently, making generalizations from these studies towards the etiology of DD can be difficult.

There are only two DTI studies done to investigate structural connectivity deficits in children with DD. These studies revealed that children impaired with DD have decreased connectivity in the right temporal-parietal areas (Rykhlevskaia et al., 2009), and the bilateral superior longitudinal fasciculus (Kucian et al., 2013). Regarding functional connectivity, there has only been the study by Rosenberg-Lee et al. (2015) who found increased functional connectivity between the IPS and fronto-parietal regions in children with DD.

Next to several connectivity deficits found in DD, a couple of above mentioned studies have also investigated neuroanatomical deficits in grey matter in individuals with mathematical disabilities and in children with DD (Molko et al., 2004; Rykhlevskaia et al., 2009). Regarding DD, studies observed decreased grey matter volume in the IPS (Ranpura et al., 2013; Rotzer et al., 2008; Rykhlevskaia et al., 2009), anterior cingulate cortex (Rotzer et al., 2008; Rykhlevskaia et al., 2009) inferior frontal gyrus and middle frontal gyri (Rotzer et al., 2008), and occipito-temporal cortex (Rykhlevskaia et al., 2009) in children.

All of above mentioned neuroimaging studies regarding the structural and neuroanatomical correlates of DD limited their focus to children and it remains to be determined whether similar abnormalities can be observed in adults with DD. In this current study, we compared the structural and functional connectivity correlates and neuroanatomical deficits of 24 adults with dysalculia and controls, matched on sex, age, IQ, reading abilities, and educational history, by analyzing measures of DTI, functional connectivity MRI, and VBM. As a wide network of brain regions is assumed to underlie numerical and arithmetic processing, we included previous studied white matter tracts in studies of numerical and mathematical cognition as well as on DD. These tracts were: one dorsal tract (Arcuate Fasciculus (AF)), two ventral tracts (ILF and IFOF), and one inter-hemispheric tract (Corpus Callosum (CC)) (for review, see Matejko & Ansari (2014)).

7.2 Materials & Methods

Participants

In total, 54 adult participants took part in this study as paid volunteers. Due to technical issues with the scanner, a useful data set was only acquired for 48 participants (all females, aged between 18 and 27 (M: 21.81; SD: 2.16), three left-handed participants with DD, and two left-handed participants in the control group), including 21 participants with DD and 23 control participants with normal achievement in mathematics. All participants had normal or corrected-to-normal vision and reported no neurological or psychiatric history. An interview with all the participants was conducted to confirm that all individuals with DD and none of the control participants met the DSM-V criteria for specific learning disorder in mathematics (DD). All participants provided two written informed consents, one before the behavioral session and one prior to scanning. The study was approved by the medical ethics committee of KU Leuven.

Matching dyscalculia group and control group

All participants successfully completed secondary school and they were either in college or university. The two groups were individually matched pairwise for their education in secondary school and college/university, gender, and age (see Table 7.1). Newt, we measured a wide range of mathematical and non-mathematical skills. Statistical analyses for all the behavioral measures were done in Matlab version 8.3.0.532 (R2014a).

Differences in mathematical abilities were assessed by three tests. Tempo Test Calculation (De Vos, 1992) and French Kit (French et al., 1963) are two timed standardized paper-and-pencil tests for one- and multi-digit calculation, respectively (including addition, subtraction, multiplication, and division). We also administered the arithmetic subtest of the WAIS (Wechsler Adult Intelligence Scale III), which involves a series of

verbally presented word problems without time pressure for each participant.

In addition, we measured reading skills, motor speed, and intelligence to ensure the groups were matched for all these measures. Reading abilities were assessed by two standardized reading tests in which as many existing words (Brus, 1999) and pseudo-words (Van den Bos, 1999) had to be read as fast as possible in one minute. Both reading scores were averaged after transformation to Z-scores. These reading tests were done to verify the absence of comorbidity with dyslexia.

Third, measures of verbal and non-verbal intelligence were obtained by means of the Vocabulary and Matrix Reasoning subtests of the WAIS, respectively.

Lastly, to ensure that any group differences in reaction time for the experimental task (number comparison) in the scanner were not due to group differences in processing speed, participants performed a motor speed task on a computer. During this task subjects had to decide, in a quick but accurate manner, on which side the stimulus with a white surface was presented, by pressing the corresponding key (De Smedt et al., 2010).

7

Structural Connectivity

Data Acquisition

For 23 control participants and 21 participants with DD DWI data were obtained. Diffusion images were acquired on a 3T Philips Ingenia CX Scanner using a single spin shot EPI with SENSE acquisition. Whole brain images were acquired with the following parameters: 58 sagittal slices, slice thickness = 2.5 mm, voxel size = 2.5 $\times$ 2.5 $\times$ 2.5 mm^3, TR = 7600 ms, TE = 82 ms, field-of-view = 220 $\times$ 240 mm^2, matrix size = 80 $\times$ 94 and acquisition time = 10 min 32 s. Diffusion gradients were applied along 60 noncollinear directions (b = 1500 s/mm^2).

Image preprocessing and tractography

Preprocessing of the raw diffusion MR data was done using ExploreDTI (Leemans et al., 2009) and contained following steps: (1) Images were corrected for eddy current distortion and subject motion; (2) a non-linear least square method was applied for diffusion tensor estimation, and (3) for each participant a whole brain tractography was estimated using following parameters: uniform 2 mm seed point resolution, FA threshold of 0.2, angle threshold of 40°, and fiber length range of 50 - 500 mm.

We used the TrackVis software to delineate white matter tracts for each participant in native space (Wang & Wedeen, 2007) for DTI tractography. Against the background of the review of Matejko and Ansari (2014) following tracts were delineated using the DTI model: genu and splenium of the CC, left and right IFOF, left and right ILF, left and right frontal to temporoparietal AF (AF_{FTP}), left and right frontal to temporal AF (AF_{FT}), left and right frontal to parietal AF (AF_{FP}), left and right temporal to parietal AF (AF_{TP}).

We extracted for all tracts following properties: the molecular diffusion rate (MD), the directional preference of diffusion (FA), the diffusion rate along the main axis of diffusion (AD), and the rate of diffusion in the transverse direction diffusivity (RD). The delineation of all the tracts for each participant of the control group was done by two independent raters. The inter-rater reliability for all tracts was calculated by intra-class correlation and ranged from 0.87 to 0.99, demonstrating a high reproducibility of the tractography.

To test for the difference in white matter connectivity between the two groups, a two sample *t*-test was done per tract and for each DTI measure (FA, MD, AD, and RD values). We corrected for multiple comparisons across tracts for each measure with FDR correction. Secondly, the association between DTI measures of the tracts and mathematical skills were assessed using Spearman's partial correlation and corrected for multiple comparisons within tracts with an FDR-correction.

Functional Connectivity

Design

The functional task-based data of this study are currently under review (Bulthé et al., 2017). The experimental runs had a short-block design with variable block duration, which was the same design as in Bulthé, De Smedt & Op de Beeck (2014). During the experimental runs, participants had to perform a number comparison task (indicate smaller or larger than five) every time the numerosity andor format (non-symbolic versus symbolic) changed, which made the participants explicitly access numerical magnitude representations (Piazza et al., 2004b). Per participant, between 8 and 12 experimental runs were acquired.

The localizer runs consisted of the same design as Bulthé, De Smedt & Op de Beeck (2014); Bulthé et al. (2015) and were used to independently from the experimental runs define the ROIs. Participants had to subtract two numbers ranging from 1 to 20 from each other and needed to indicate if the solution was even or odd. Two localizer runs were obtained per participant.

Data acquisition

For 48 participants, the fMRI data was acquired in a 3T Philips Ingenia CX Scanner with a 32-channel head coil using a T2*-weighted EPI sequence (50 slices, 2.10 $\times$ 2.15 mm in plane acquisition voxel size, slice thickness 2 mm, interslice gap 0.2 mm, TR = 3000 ms, TE = 30 ms, flip angle = 90, 100 $\times$ 97 acquisition matrix). For each participant also a T1-weighted anatomical volume was obtained (182 slices, resolution 0.98 $\times$ 0.98 $\times$ 1.2 mm, TR = 9.6 ms, TE = 4.6 ms, 256 $\times$ 256 acquisition matrix).

Regions of interest

Superior and inferior frontal gyrus (SFG, IFG), superior and inferior parietal lobule (SPL, IPL), fusiform gyrus (FG), inferior occipital cortex (IOC), and primary visual

cortex (PVC) were delineated with an anatomical mask in the WFU PickAtlas Toolbox (Wake Forrest University PickAtlas, `fmri.wfubmc.edu/cms/software`). We selected the voxels based on the conjunction of the voxels in that mask that survived the functional contrast (task minus fixation) from the independent localizer scans at an uncorrected threshold at $p < 0.001$. For the IPS there was no anatomical mask available in the WFU PickAtlas Toolbox, so we delineated this ROI manually on the functional contrast of the localizer scans (uncorrected threshold at $p < 0.01$). All ROIs were created at individual level.

Analyses

Preprocessing steps for this analysis comprised (1) bandpass filtering between 0.01 and 0.2 Hz (Balsters et al., 2016; Baria et al., 2013), (2) regression of head motion parameters and their first derivatives (3) regression of white matter and ventricle signals and their first derivatives (Ebisch et al., 2013), (4) regression of task-related BOLD fluctuations (task = the contrast 'task minus baseline') (Boets et al., 2013; Ebisch et al., 2013), (5) scrubbing of motion-affected functional volumes (Power et al., 2012), and (6) spatial smoothing at 4 mm FWHM.

We obtained a representative BOLD time course for each ROI by averaging the time courses of the voxels within the ROI. For each participant we then created a functional connectivity matrix by calculating Pearson cross-correlations between the BOLD time courses of each pair of ROIs. After converting the single-subject matrices to Z-scores by means of the Fisher's r-to-Z transformation, we calculated a group-level matrix by conducting a random effects analysis across subjects ($p_{\text{FDR}} < .001$). Group-level comparisons among functional connectivity scores were performed by calculating independent-sample t tests on the Z-score matrices ($p_{\text{FDR}} < .05$).

Voxel-Based Morphometry

The VBM analysis was performed with SPM12 and according to the methodological description of (Ashburner & Friston, 2000) for the standard VBM analysis (Good et

Table 7.1: Descriptive statistics on matching variables.

	DD Group	**Control Group**	$\mathbf{t}_{46}$	$\boldsymbol{p}$
Descriptive Information				
N	24	24	-	-
Age (in years)	21.96 (2.16)	21.67 (2.20)	0.46	0.65
Mathematical Abilities				
French Kit	35.00 (7.97)	54.50 (15.86)	5.38	<0.0001
Tempo Test Arithmetic	113 (17.46)	148.75 (21.92)	6.25	<0.0001
Arithmetic (WAIS)*	7.50 (2.06)	10.79 (2.21)	5.34	<0.0001
Reading				
Z-score Reading	-0.20 (1.12)	0.20 (0.62)	1.49	0.14
IQ Measures				
Nonverbal - Matrix reasoning (WAIS)*	9.08 (2.90)	10.23 (3.01)	1.32	0.19
Verbal - Vocabulary (WAIS)*	10.79 (2.99)	12.08 (2.26)	1.69	0.10
Motor Speed Task				
Accuracy (%)	96.88 (10.82)	98.75 (2.21)	0.83	0.41
Reaction times (ms)	399.4 (0.08)	362.4 (0.06)	-1.80	0.08

Standard deviations are shown in parentheses. * Standardized score with M = 10 and SD = 3.

al., 2001). The structural MRI images of all participants were spatially normalized to Talairach space and resliced to a voxel size of 1 mm^3 isotropic. The resliced images were partitioned into grey matter, white matter, cerebrospinal fluid, and other compartments. Grey matter segments were smoothed with a 12-mm FWHM isotropic Gaussian kernel. Statistical analysis for comparing grey matter volume between the two groups was performed by a two-sample *t*-test with global normalization for total amount of grey and white matter (threshold of $p < 0.05$ after FWE correction). A Spearman correlation was applied to investigate the correlation of the grey matter density and mathematical performance.

7.3 Results

7.3.1 Behavioral data

Table 7.1 shows neuropsychological profiles of the DD group and the control group. The two groups differed significantly on mathematical abilities as assessed by the Tempo Test arithmetic, French Kit, and WAIS Arithmetic. They did not differ in IQ, age, reading ability, and motor speed.

7.3.2 Structural Connectivity

None of the tracts that were investigated with the DTI model showed a significant group difference (even without correction for multiple comparisons) for FA: AF_{TP} right ($t_{1,42}$ = -1.68, p_{FDR} = 0.41), AF_{TP} left ($t_{1,42}$ = -0.78, p_{FDR} = 0.77), AF_{FP} right ($t_{1,42}$ = -0.17, p_{FDR} = 0.91), AF_{FP} left ($t_{1,42}$ = 1.41, p_{FDR} = 0.46), AF_{FT} right ($t_{1,42}$ = -1.61, p_{FDR} = 0.41), AF_{FT} left ($t_{1,42}$ = -0.80, p_{FDR} = 0.77), AF_{FTP} right ($t_{1,42}$ = -0.67, p_{FDR} = 0.79), AF_{FTP} left ($t_{1,42}$ = 0.13, p_{FDR} = 0.91), CC posterior ($t_{1,42}$ = -0.24, p_{FDR} = 0.91), CC anterior ($t_{1,42}$ = 0.93, p_{FDR} = 0.77), ILF right ($t_{1,42}$ = 0.55, p_{FDR} = 0.82), ILF left ($t_{1,42}$ = 0.11, p_{FDR} = 0.91), IFOF right ($t_{1,42}$ = -1.85, p_{FDR} = 0.41), and IFOF left ($t_{1,42}$ = -1.72, p_{FDR} = 0.41) (Figure 7.1).
For the other DTI measures, we also did not found a significant group effect: for AD *t*-values ranged from -1.85 to 0.82 ($0.54 < p_{FDR} < 0.99$); for MD *t*-values ranged from -0.92 to 0.90 (all p_{FDR}'s = 0.97); and for RD *t*-values ranged from -0.79 to 1.39 ($0.89 < p_{FDR} < 0.98$).

Because no group differences were observed in the DTI measures, the associations between these measures and mathematical performance (French kit, Tempo Test Arithmetic, and Arithmetic (WAIS)) was analyzed by combining the two groups. For FA no significant correlations with any of the behavioral math measures were observed in any of the tracts: correlations ranged for French kit from -0.25 to 0.15 (all p_{FDR}'s = 0.90), for Tempo Test Arithmetic from -0.22 to -0.18 ($0.22 < p_{FDR} < 0.97$), and for Arithmetic (WAIS) from -0.18 to 0.11 (all p_{FDR}'s = 0.99). A similar pattern of findings were observed for AD (*r*s ranged from -0.23 to 0.11, $0.15 < p_{FDR} < 0.99$), MD (*r*s ranged from -0.21 to -0.05, $0.26 < p_{FDR} < 0.99$), and RD (*r*s ranged from -0.23 to 0.09, $0.37 < p_{FDR} < 0.99$).

7.3.3 Functional Connectivity

A functional connectivity analysis was performed to test which ROIs were functionally coupled with each other and whether this coupling differed between the two groups. For both groups, all the pairwise functional connectivity strengths were significant

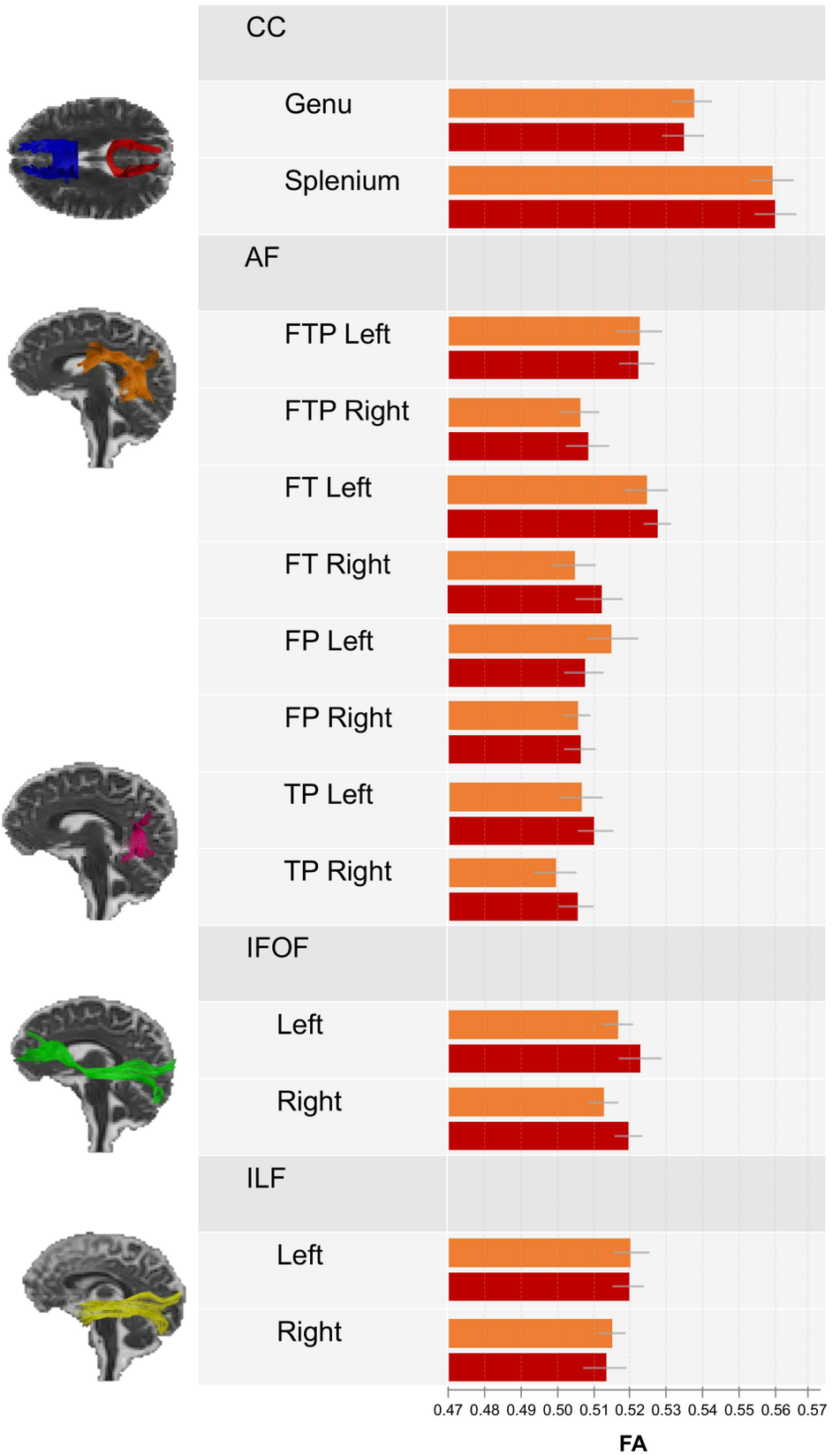

Figure 7.1: Overview of the DTI results. Mean FA values of the tracts in the control group (orange) and DD group (red). Error bar depict standard deviation.

(controls: $10.92 < t_{23} < 38.81$, all p_{FDR}'s < 0.001; DD: $12.80 < t_{23} < 37.58$, all p_{FDR}'s < 0.001) (Figure 7.2a-b). For the individual connections between ROIs, there were significant group differences for the connectivity between PVC and IOC ($t_{1,46}$ = -3.17, p_{FDR} = 0.04) and between PVC and FG ($t_{1,46}$ = -3.47, p_{FDR} = 0.03) with higher connectivity in individuals with DD than in controls (Figure 7.2c).

To test if this hyper-connectivity between visual regions as observed in our sample with DD was related to numerical processing, we correlated the functional connectivity strength between these ROIs and behavioral numerical measures (French Kit, Tempo Test Calculation, WAIS-Arithmetic) in both groups. We found for WAIS Arithmetic a significant correlation with the functional connectivity of PVC and IOC (r = -0.32, p = 0.03) and PVC and FG (r = -0.32, p = 0.03). We also found a negative trend the correlation between French Kit and the functional connectivity between PVC and IOC (r = -0.28, p = 0.06) and PVC and FG (r = -0.27, p = 0.07). For Tempo Test Arithmetic, there was no significant correlation with the functional connectivity between PVC and IOC (r = -0.16, p = 0.27) and PVC and FG (r = -0.21, p = 0.15).

7.3.4 Voxel-Based Morphometry

We performed a VBM analysis to investigate whether any brain regions showed structural differences. Only an increase in grey matter in the left Posterior Cingulate Cortex (PCC) ($t_{1,46}$ = 5.27, p_{FWE} = 0.04, MNI coordinates: -22 -48 25) was observed in DD compared to controls. No other differences were found (Figure 7.3).

7.4 Discussion

The current study is the first neuroimaging study to look into the structural and functional connectivity and anatomical correlates of DD. We found no differences in any of the white matter tracts (four in total with 17 segments) between adults with and without DD. However, we did observe increased functional connectivity in temporo-occipital regions and increased grey matter volume in PCC in DD.

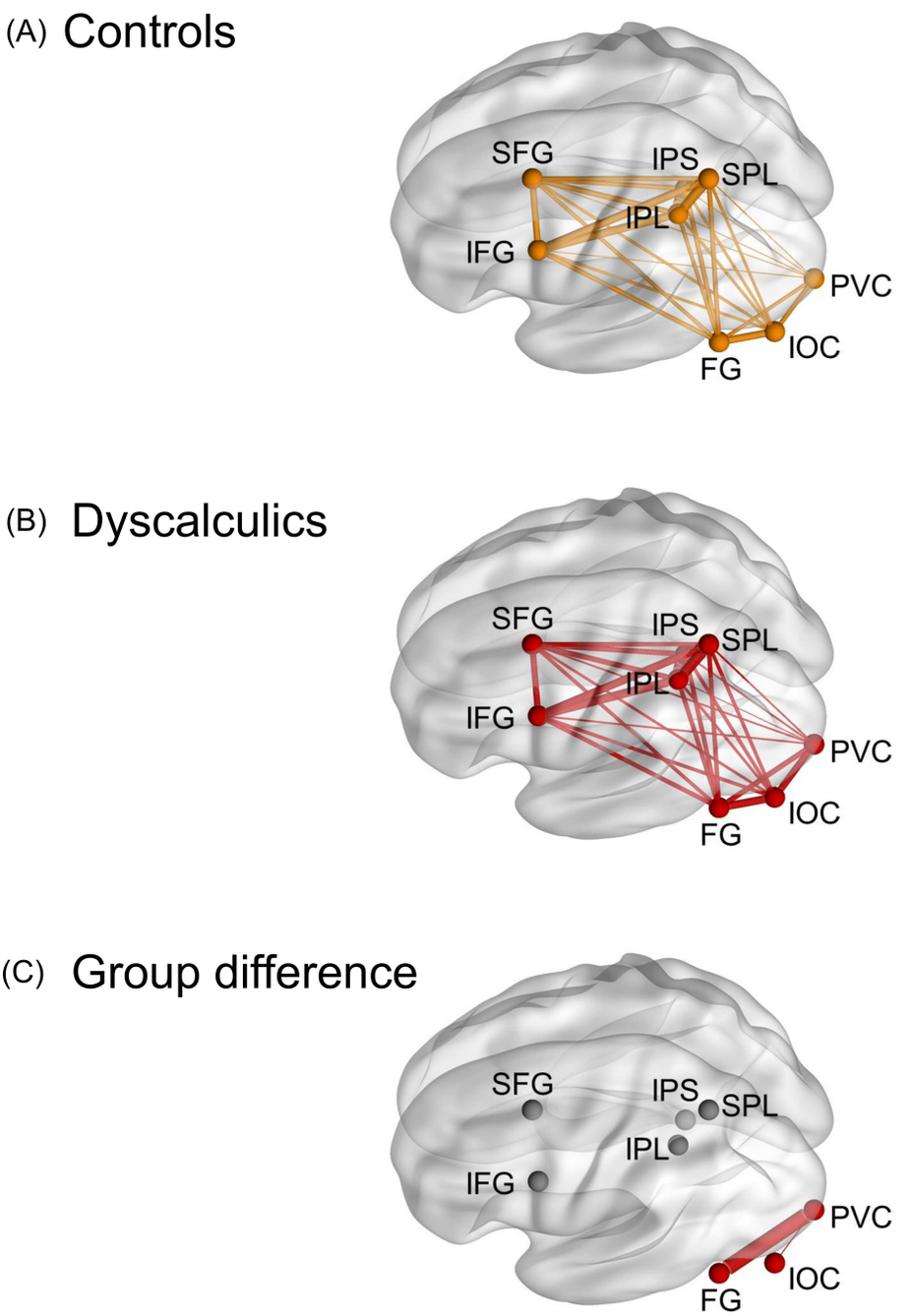

Figure 7.2: Overview of the functional connectivity results. All the ROIs were significantly functionally connected with each other for the (A) control participants and (B) participants with DD at a FDR ($p < 0.001$) corrected level. (C) We observed a significant group difference at FDR ($p < 0.05$) corrected level with higher functional connectivity for DD between PVC and IOC and between PVC and FG.

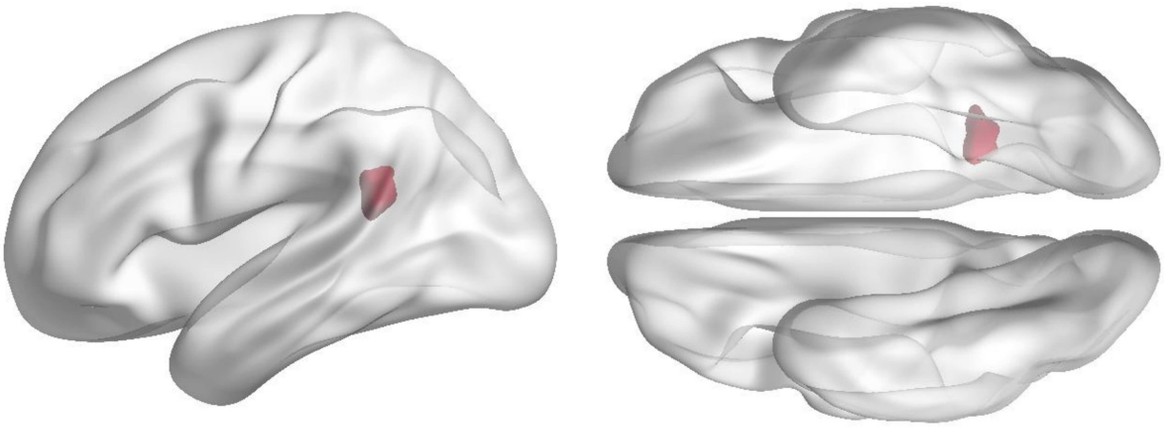

Figure 7.3: Brain region where adults with DD showed significant more grey matter, compared to adults without DD.

In contrast to the functional connectivity differences in this study, we did not observe any structural connectivity differences in any of the tracts previously related to numerical processing (Matejko & Ansari, 2014). This is in contrast to two previous studies who found that children with DD had decreased connectivity in the right temporal-parietal areas (Rykhlevskaia et al., 2009), and the bilateral superior longitudinal fasciculus (Kucian et al., 2013). There are two possible explanations for the discrepancy in findings between our study and previous ones. First, we have a very strict matching between adults with and without DD, namely by controlling not only for sex, age, and intelligence, but also for educational history and environment. This strict matching can explain why we did not replicate previous neuroimaging studies. However, this strict matching is essential to dedicate the observed differences to DD and not to possible differences in education. Second, it might be the case that the white matter deficits correlated with DD in children are only present early in development, and that over time these white matter deficits in DD become very small or even negligible.

In line with the only previous functional connectivity study in children with DD (Rosenberg-Lee et al., 2015), we found hyper-connectivity in adults with DD between FG and PVC and between IOC and PVC. These regions are known to be involved in the processing of complex visual objects (Grill-Spector et al., 2008; Menon et al., 2000). It has been previously demonstrated that children with DD had decreased

grey matter volume in these regions (Rykhlevskaia et al., 2009). Furthermore, the observed increased connectivity in this study was related to arithmetic skills, namely, more functional connectivity is associated with lower arithmetic skills.

We suggest that these findings of increased functional connectivity might be interpreted in terms of compensatory processes that were activated during digit number processing in DD. More specifically, these increased functional connectivity from the occipital cortex to the infero-temporal cortex can be related to increased connectivity to the "visual number area" (located in the infero-temporal cortex). This area was first mentioned by Shum et al. (2013) who did intracranial electrophysiological recordings. Shum and colleagues (2013) demonstrated that this area responds more strongly to digits than to control conditions which are well-matched in terms of visual (letters, false fonts), semantic (number words) or phonological (phonologically similar non-number words) similarity. Furthermore, Srihasam et al. (2012) did a fMRI study in macaque monkeys and observed as well an area in the ventral temporal cortex selective for trained symbols (opposed to untrained shapes and faces). These results could suggest that such regions only develop when a high level of visual proficiency with number symbols is reached (as was the case for the younger monkeys in that study) (Piazza & Eger, 2016). Therefore, we suggest that the, in this study, observed increased connectivity in direction of the inferior-temporal cortex is caused by compensation mechanisms in DD to process Arabic digits. Note however that we dit not study the exact location of "visual number area", as this region lies within or close to the fMRI signal-drop out zone produced by the nearby auditory canal and venous sinus artifacts Shum et al. (2013).

In line with previous studies in children (Rotzer et al., 2008; Rykhlevskaia et al., 2009), we found grey matter volume abnormalities for adults with DD in PCC. The PCC is known to be a part of the Default Mode Network (DMN). The DMN is typically deactivated during cognitive demanding tasks and assumed to be involved in efficiently processing external information and supporting mental activity that is internally directed (Raichle, 2015). Our findings in adults might be consistent with the

interpretation of (Rosenberg-Lee et al., 2015) that their findings are related to a possible deficit in the default mode network. However, important to note is that, against our expectations, we did not observe any anatomical abnormalities in the parietal cortex or the IPS in contrast to previous studies (Ranpura et al., 2013; Rotzer et al., 2008; Rykhlevskaia et al., 2009).

Recently, there is an increasing awareness that the neural origins of DD are not restricted to domain-specific deficits such as impaired neural number representations. Instead, or in addition, the neural correlates might also include domain-general deficits and involve impairments that are not specific to math (Fias et al., 2013; Rubinsten & Henik, 2009; Wilson et al., 2015). Moreover, mathematical skills are related to deficits in working memory (Rotzer et al., 2009; Szucs et al., 2013), inhibition (Bull et al., 1999), attention (Shalev et al., 1995), and executive functions (Ashkenazi & Henik, 2010). Furthermore, mathematical deficits are often accompanied by low IQ and other cognitive deficits (von Aster & Shalev, 2007). Therefore, impairments in these domain-general cognitive functions have been highlighted as potential risk factors for learning disorders and their comorbidity (Rubinsten & Henik, 2009).

The neuroanatomical structural and functional connectivity deficits in adults with DD in this study fit into the domain-general deficits of DD. The deficits observed in this study are not located in the IPS and parietal regions. As in previous studies, we demonstrated the neural deficits correlated with DD are observed outside the parietal cortex as well (Kaufmann et al., 2011; Rosenberg-Lee et al., 2015; Rotzer et al., 2008; Rykhlevskaia et al., 2009). Our functional connectivity results showed hyper-connectivity for DD between visual regions and FG. Interestingly, increased functional connectivity was previously linked to compensation processes and inhibitory processes (Geerligs et al., 2012; Rosenberg-Lee et al., 2015). Structural differences were located in the PCC, a brain region that is part of the DMN which is also linked to domain-general processes.

7.5 Conclusion

To conclude, by the application of a different neuroanatomical techniques (DTI, fcMRI, and VBM), we demonstrated both functional connectivity impairments in occipito-temporal regions and increased grey matter in posterior cingulate cortex in adults with DD. However, we did not found any of the structural connectivity deficits observed in previous studies in children with DD. Nevertheless, our findings are consistent with theoretical proposals that most neurodevelopmental disorders arise from a combination of diffuse functional disruptions, deficits in connectivity between regions, and anatomical differences (Johnson et al., 2002; Menon, 2011).

Acknowledgments

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Part IV

Arithmetic skills and number processing

8 Arithmetic skills correlate negatively with overlap of symbolic and non-symbolic number representations

The contributions of the first author are:

- Literature study
- Perform analyses on empirical data
- Co-interpretation of empirical results
- Co-formulation of conclusions
- Text redacting

Final stage before submission

Bulthé, J., De Smedt, B., & Op de Beeck, H. (2017). Arithmetic skills correlate negatively with overlap of symbolic and non-symbolic number representations.

8.1 Introduction

Adults, children, infants, and even animals are capable of discriminating between non-symbolic numerosities (e.g. tree vs. sixteen apples) in a basic, and probably innate manner (Dehaene & Cohen, 1997). Humans also acquire, symbols, such as Arabic digits, to refer to such numerosities. It remains an open question on how these symbolic numbers acquire their meaning and how symbolic and non-symbolic representations of number are linked to each other (for review, see Leibovich & Ansari (2016)).

According to the mapping account, symbolic number representations acquire their meaning by being mapped onto the preexisting, non-symbolic representations of number (Piazza et al., 2010). Recent advances in the analysis of functional brain imaging data allow us to directly investigate whether the content of these two types of neural representations indeed overlap via MVPA. As such, one can directly test whether the differences between activation patterns for different numerosities in a non-symbolic format generalize to the differences between activation patterns in a symbolic format. The findings using this method have been mixed. One study showed a small generalization in parietal cortex (Eger et al., 2009), but others reported no generalization and thus completely independent (yet co-localized) representations for numerosities in the different formats (Bulthé, De Smedt & Op de Beeck, 2014; Damarla & Just, 2012). In addition, the representation of non-symbolic numbers in parietal cortex and IPS seems to be strongly related to visual properties of the stimuli rather than abstract numerosity (Bulthé et al., 2015).

A more recent account might explain why this mapping between symbolic and non-symbolic formats is not necessarily very strong. This estrangement account argues that in early childhood symbolic representations acquire their meaning through mapping onto non-symbolic representations of number, however, over the course of de-

velopment and with increasing arithmetic skills these symbols become “estranged” from the non-symbolic representation (Lyons et al., 2012). This latter account makes a specific prediction about which relationship one could expect between strength of the mapping between non-symbolic and symbolic representations at the neural level and arithmetic skills. The better the arithmetic skills, the higher the estrangement and thus the weaker the relationship between symbolic and non-symbolic representations.

8.2 Material & Methods

We noticed such a relationship when comparing data from several recent experiments from our lab. This comparison provided us with data from a relatively large sample of adults that show a large variability in their arithmetic skills and experience. All participants were scanned with the exact same experimental design analyzed with MVPA fMRI. All completed a standard timed test of arithmetic (French et al., 1963) to measure their arithmetic skills. In total, this provided us with three participant groups with different levels of arithmetical skill and experience. The first participant group, from Bulthé, De Smedt & Op de Beeck (2014), comprised 15 adults with High arithmetic skills and experience (HS) (e.g. engineers and PhD students in Psychology). The second and the third group came from a recent study by Bulthé et al. (2017) (currently under review). The second group comprised 24 adults with Average arithmetic skills and experience (AS) (e.g. university undergraduates in social sciences). The third group comprised 24 adults with DD and had very low arithmetic skills, yet matched with the second group in terms of their level of education. All group of participants completed the same neuroimaging design as in Bulthé, De Smedt & Op de Beeck (2014). The design comprised a number comparison task in the scanner with numerosities 2, 4, 6, and 8 in both non-symbolic and symbolic format. A localizer task, during which participants had to calculate, was acquired to select the main ROI that was the focus of analyses in the aforementioned landmark study of Eger et al. (2009): parietal cortex.

We applied MVPA generalization to specifically test if representations of both formats are overlapping in the parietal cortex. With this technique we trained a classification model to distinguish the neural representations of for example, symbolic digits 2 and 4. Once trained, we feed the model with the neural representations of the same numerosities but in the different format (e.g. non-symbolic numbers 2 and 4). Afterwards, we averaged across all pairwise comparisons and both generalization directions for each participant group. The estrangement account predicts limited generalization between both formats, and most importantly a decrease in generalization with increasing arithmetic skills and/or increasing arithmetic experience. This negative association between generalization and arithmetic skills was tested via a linear regression analysis (group as predictor and generalization accuracy as dependent variable) and a spearman correlation between generalization accuracies and the behavioral arithmetic tests.

8.3 Results

In the parietal cortex, there was no significant generalization between formats in the HS group (t_{14} = -1.22, p = 0.24) (Figure 8.1). In contrast, there was a significant generalization between formats in parietal cortex in the AS (t_{23} = 3.21, p = 0.004) and DD (t_{23} = 4.18, p = 0.0004) group. The results in parietal cortex clearly showed a significant linear trend with an increase in generalization coupled with a decrease in arithmetic skills (linear regression analysis, Y = generalization accuracy, X = arithmetic skills, R^2 = 0.15, p = 0.002). Furthermore, there was a significant negative correlation between the degree of generalization and the arithmetic test (rho = -0.23, p = 0.04, one-sided test).

Eger et al. (2009) already suggested that a large ROI covering all/most of parietal cortex has to be tested to find evidence for generalization. They found no generalization in smaller clusters. Our results converge with theirs. In particular, when restricting the analyses to IPS, decoding went down overall (Bulthé, De Smedt & Op de Beeck, 2014; Bulthé et al., 2015) as did generalization. None of the groups showed generalization accuracy in IPS (HS: t_{14} = -0.42, p = 0.68; AS: t_{23} = 0.64, p

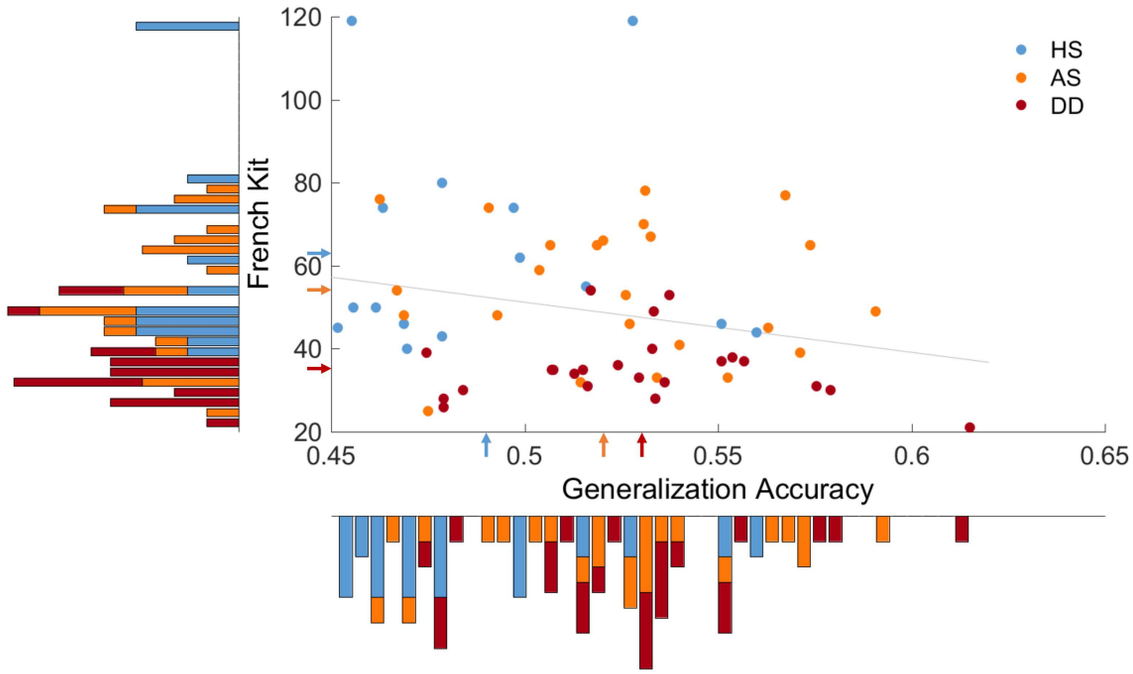

Figure 8.1: Overview of the results. The scatterplot shows the relation between generalization accuracy (X-axis) and the arithmetic skills measured with French Kit (Y-axis). The arrows on the axis represent the group means for generalization accuracy (X-axis) and French Kit (Y-axis). The grey line represents the linear trend between the generalization and arithmetic skills. Histograms represent the probabilities for each group for generalization (X-axis) and French kit (Y-axis).

$= 0.53$; DD: $t_{23} = 1.43$, $p = 0.17$), nor was there any trend towards an association between generalization and group membership ($R^2 = 0.02$, $p = 0.27$), or arithmetic skills and the generalization (rho = -0.14, $p = 0.13$, one-sided test).

8.4 Discussion

To conclude, the results in the parietal cortex demonstrated a strong relationship between the degree of overlapping neural representations between format (e.g. generalization accuracy) and the level of arithmetic skills and experience.

In our tests we have tested the relationship with arithmetic skills. However, in these conclusions as well as in the explanation of the estrangement account, we have deliberately referred to “skills and experience”. The two are probably correlated, but not necessarily the same. The most convincing argument for a potential discrepancy

is the generalization performance in the AS group. In terms of arithmetic skills, the AS group is between the two groups and clearly very different from the DD group (French Kit HS vs AS: $t_{37} = 1.68$, $p = 0.10$; HS vs DD: $t_{37} = 5.42$, $p < 0.001$; AS vs DD: $t_{46} = 5.38$, $p < 0.001$). However, in terms of generalization, the AS group is almost identical to the DD group. Interestingly, the AS and DD groups are very well matched in how much they use arithmetic in their everyday life, which for most of them was a bachelor or professional degree with a relatively limited amount mathematics. This suggests that generalization would be more related to arithmetic experience rather than to arithmetic skill, although this hypothesis needs further empirical testing. With our study we cannot formally differentiate between these two correlated factors. Most importantly, whatever factor would turn out to be most important, the findings would remain in line with the predictions of the estrangement account.

Leaving this uncertainty aside from now, our results indicate that individuals with lower or impaired arithmetic skills have an increased association between symbolic and non-symbolic number representations, while individuals with higher arithmetic skills do not have these overlapping neural representations. Thus, individuals with more experience in arithmetic symbols have symbolic representations which have a separate meaning from the quantity it represents. This might be much more efficient when doing basic arithmetic, but also advanced mathematics or calculating with fractions. Recent research has shown that expert mathematicians calculating with fractions indeed rely much more on the algebraic expression of the fraction rather than the quantity of the numerator and denominator of the fraction (Obersteiner et al., 2016).

Important to note, is that these higher generalization accuracies in individuals with average or lower arithmetic skills are not driven by higher decoding accuracies of symbolic and non-symbolic numbers. On the contrary, the individuals with higher mathematical skills have higher decoding accuracies for numbers in the parietal cortex than the individuals with average (Bulthé, De Smedt & Op de Beeck, 2014) and lower arithmetic skills (Bulthé et al., 2017).

These new insights have important implications for learning strategies in elementary schools and interventions for children with lower mathematical skills, as they often consist of learning the meaning of symbols through non-symbolic numbers, and probably subsequently increasing their neural association which can explain our results. More research is needed to further investigate the influence emphasizing the relation between symbolic and non-symbolic numbers in education and interventions for DD.

Acknowledgments

This work was supported by the Fund for Scientific Research Flanders (fellowship to J.B, an IDO Project of the KU Leuven (IDO/10/003), an FWO project (G.0946.12), a Federal Research Action (IUAP-P7/11), and an ERC grant (ERC-2011- Stg-284101). We thank the consultants of PraxisP (KU Leuven, Belgium) for their help in the recruitment of participants with dyscalculia.

Part V

General conclusions and perspectives

9 General conclusions and perspectives

"The important thing is to never stop questioning."

– Albert Einstein

The global objective of this dissertation was the advancement of our understanding of the neural correlates of typical and atypical number processing by applying advanced neuroimaging techniques. The application of these advanced techniques have empowered us to directly address several debates in the numerical cognition field.

- **Debate 1**: The main challenge when investigating basic number processing, is that one quantity can be presented in different formats: symbolic (e.g. "2") or non-symbolic (e.g. "●●"). It has been questioned in literature whether or not these symbolic and non-symbolic numbers are represented at a format-independent manner in the human cortex. In chapter 4 and chapter 5 we demonstrated that symbolic and non-symbolic numbers do not share overlapping neural representations and that any representational similarities between them are linked to the number of visual objects present in the format.

- **Debate 2**: Two theories of the etiology of DD have been proposed in the last decade. One theory suggests that the neural number representations are impaired in DD. On the other hand, another theory proposed that the access to these neural number representations is impaired. In chapter 6 and chapter 7, we tested both theories and found that the neural etiology of DD is more complicated and does not fit into one theory. We found impaired representations, connectivity differences, and anatomical abnormalities in adults with DD compared to controls.

- **Debate 3**: Currently it is debated how symbolic numbers acquire their meaning. Are they mapped onto the neural representations of non-symbolic numbers? Or, does this mapping only happen in the beginning of development of symbolic skills and over the coarse of years both formats become estranged? In chapter 8, we demonstrated a negative correlation between arithmetic skills and the neural overlap between symbolic and non-symbolic number representations. This finding fits into the estrangement theory suggesting that with better

arithmetic skills the association between symbolic and non-symbolic number processing becomes less strong.

For the remainder of this chapter, we will discuss our findings regarding these debates, methodological considerations, and future research directions.

9.1 Conclusions and considerations

9.1.1 Number representations in the human cortex

The first study (chapter 4) applied MVPA fMRI to look into the neural representations of dots and digits and questioned if these neural representation of digits and dots are overlapping on three different spatial scales (entire lobules, smaller regions of interest and a searchlight analysis with 2-voxel radius). Results showed that numbers in both formats were decodable in occipital, frontal, temporal and parietal regions. However, there were no overlapping representations between dots and digits on any of the spatial scales. These data suggest that the human brain does not contain an abstract representation of numerical magnitude.

In chapter 5, we further investigated the nature of the association between digits and dots at a neural level. In line with studies on object cognition, which reported that the IPS processes the number of objects presented (Song & Jiang, 2006; Todd & Marois, 2005; Vogel & Machizawa, 2004; Y. Xu, 2008; Y. Xu & Chun, 2007b), our data suggest that Arabic digits are more related to one dot than to dot patterns with corresponding numerical magnitude. This significant finding contradicts again the hypothesis that numbers are processed in a format-independent manner in the human parietal cortex.

Taken together, our first two studies strongly contradict the previously published neuroimaging evidence in favor of the presence of an abstract number coding mechanism in the human cortex (see chapter 1, for a meta-analysis and review see Ansari (2008); Nieder & Dehaene (2009)). However, several considerations regarding the studies discussed in chapter 4 and chapter 5 need to be addressed.

Considerations

The possible influence of low-level stimuli properties Although our studies controlled the non-symbolic stimuli for low-level stimuli properties (e.g., overall number of pixels), we only controlled for one visual variable at the time, leaving open the possiblity that visual properties of the stimuli changed accordingly with the number (Gebuis & Reynvoet, 2012b). This might influence our results, as Gebuis & Reynvoet (2012b) demonstrated that people cannot extract number from a visual scene independent of its visual cues. Instead, number judgments are based on the integration of information from multiple visual cues. Gebuis and colleagues concluded (p642): "The existence of an approximate number system that can extract number independent of the visual cues appears unlikely. We therefore propose that number judgment is the result of the weighing of several distinct visual cues." As we found significant decoding accuracies in the occipital cortex, one might wonder whether this has to do with *only visual properties* and not with number itself. However, a recent EEG study by Park et al. (2015) demonstrated a stronger modulation of visual responses for changes in numerosity than for visual properties of the number. These findings provide evidence, that it might be the case that the visual system is not relying explicitly on visual properties to encode the numerosity.

The use of a direct number comparison task We failed to replicate the earlier findings of Eger et al. (2009) demonstrating cross-format generalization in the parietal cortex. Recently, two possible explanations were given by Piazza & Eger (2016) to account for the differences between the study of Eger et al. (2009) and our study. First, the paradigm differed between the two studies. While we applied a direct number comparison task, Eger et al. (2009) applied a delayed number comparison task (first the sample was shown, a couple of seconds later the second number) separating the number representation from the comparison process. However, it is important to remark that our failure to detect any overlapping representations by multivariate analyses was also found in two other studies, using other paradigms. Damarla & Just (2012) used a passive-viewing task and did not demonstrate significant cross-format

generalization. Furthermore, Lyons et al. (2015) applied, as Eger et al. (2009), a paradigm where a temporal separation between the to-be-compared stimuli and found no overlapping neural representations by applying representational similarity analysis.

A second difference between our studies and the one of Eger and colleagues (2009), Eger et al. (2009) used a higher spatial resolution in their study compared to our studies. However, Piazza & Eger (2016) concluded that "these slight differences in imaging parameters across studies might not be critical."

Failure to generalize, a null result as well Another important consideration, is that the absence of evidence may not be confused with evidence for absence. The failure to find cross-format generalization (chapter 4) (format-dependent hypothesis) is as much a null-result as the similar brain activity between digits and dots in the IPS (format-independent hypothesis).

However, in chapter 5, we directly addressed this issue by investigating the classification rates during the generalization classification between digits and dots. Two scenarios were considered in this chapter: (a) if a *significant* generalization accuracy would be observed between digits and dots, this would confirm with significant results the notion of format-independent neural number representations; or (b) if the generalization between digits and dots failed, but the digits would be *significantly* more classified as one dot instead of the dot condition with which the digit shares the numerical magnitude, this would confirm with significant results the format-dependent hypothesis of number representations.

We observed the latter scenario in chapter 5, namely digits were significantly more classified as one dot and not as the dot condition with the same numerical magnitude symbolized by the digit. These results were consistently obtained for different digits in IPS, its subregions, and many other brain regions. This means that the nature of the neural association between digits and dots is defined b the number of objects

presented in a certain number format, than by the quantity that number represents.

9.1.2 Neural correlates of dyscalculia

Chapter 6 directly compared the quality of symbolic and non-symbolic number representations in adults with and without DD. Our results did not reveal any differences in number processing related brain activation between both groups, but did demonstrate that adults with DD have less precise non-symbolic number representations in the parietal, temporal, and frontal cortex. It was the first neuroimaging study that investigated the quality of number representations in adults with DD and the first neuroimaging study that directly investigated the quality of number representations via the application of MVPA in DD.

In chapter 7, we investigated if adults in DD have connectivity (functional and structural) and anatomical deficits in the entire cortex. Previous studies have demonstrated altered structural and functional connectivity and anatomy in children with DD (Rykhlevskaia et al., 2009; Rosenberg-Lee et al., 2015; Rotzer et al., 2008, 2009), however, to date it was not yet clear if these deficits can also be observed in adults with DD. We found no difference in structural connectivity in adults with DD, increased functional connectivity between temporo-occipital regions, and increased grey matter in a regions of the default mode network.

These two chapters on DD applied many different neuroimaging techniques to investigate the brain function (Univariate, MVPA, searchlight analysis, and subject classification), connectivity (DTI and fcMRI), and anatomical (VBM) correlates of DD in adults. Together, they illustrated the advantages of combining different imaging techniques on a whole brain level to disentangle the etiology of neurodevelopmental disorder compared to focusing on only one brain region and/or only one neuroimaging method. Namely, because of our multi-method approach, we demonstrated that the deficits in dyscalculia cannot be localized to one brain region or to one particular type of brain deficit (functional, anatomical or connectivity). We therefore suggest

future studies to apply multi-method approaches to investigate neurodevelopmental disorders and mental disorders at large, in adults as well as children.

However, there are some considerations that need to be discussed regarding the findings and methods used in these two chapters.

Considerations

Absence or undetectable impairments in symbolic number representations The two main theories regarding DD (see chapter 1, section 1.2.1.) both predict impaired symbolic number representations in DD. However, in chapter 6 we were not able to observe a significant difference in the quality of symbolic number representations. This absence of a significant difference does not necessarily mean that symbolic representations are not impaired in DD. In the following paragraph, we discuss three possible reasons for undetected impaired symbolic number representations: lack of power for the detection of symbolic number representations, range of the used symbolic magnitudes, symbolic number representations are located in a brain region outside the scanning range.

First, the lack of a significant group difference in the decoding of symbolic numbers might be due to power issues, in the sense that we may not have had enough data to be able to detect a possible underlying group difference. To investigate this possibility, we ran a classifier for the non-symbolic numbers data of chapter 6, but this time with the bare minimum of data necessary to run a classifier (two runs per participant, one run to train the classifier and one run to test the classifier). As a result of this data reduction for non-symbolic numbers, the decoding accuracies of non-symbolic numbers dropped to the level of decoding accuracies of symbolic numbers. If then the significant group effect for non-symbolic numbers would also disappear, even though we know it is present when enough data is available, it suggests that we might not have had enough data available for symbolic numbers to detect a group difference in the quality of symbolic number. The results showed a trend towards a group difference

for non-symbolic numbers (stronger than the group effect for symbolic numbers), but it failed to reach conventional levels of statistical significance ($t_{46} = 1.97$, $p = 0.06$). These results suggest that we might lack enough data for symbolic numbers to detect a possible underlying group difference or the group difference in symbolic numbers is simply smaller.

Second, our number comparison task comprised symbolic numbers 2, 4, 6, and 8. It is possible that the processing of these small digits are fully automatized in these adults (Brankaer et al., 2016) and therefore harder to pick up their neural representations. It might also explain why we, and previous multivariate studies on numerical number representations (Eger et al., 2009; Damarla & Just, 2012), observed much lower decoding accuracies for symbolic numbers than for non-symbolic numbers.

Third, it could be that the impaired symbolic number representations are located in the "visual number area", a region in the inferior temporal cortex (Shum et al., 2013) which fell outside our scanning range. This area was first described in an electrophysiological recordings study by Shum et al. (2013). Shum and colleagues (2013) demonstrated that this area responds more strongly to digits than to well-matched control conditions (letters, false fonts, number words, or phonologically similar non-number words). Furthermore, in chapter 7 we observed a hyper-connectivity from occipital regions towards the inferior temporal cortex. This might be a sort of compensation mechanism to overcome the possible impaired symbolic number representations in DD.

A major drawback with this region, according to Shum and colleagues (2013), is that this region lies within or close to the fMRI signal-drop out zone produced by the nearby auditory canal and venous sinus artifacts and is therefore often overlooked in human fMRI studies (Shum et al., 2013). However, more recently Abboud et al. (2015) located this region with fMRI in blind participants by presenting symbolic numbers via visual-to-music sensory-substitution device. They observed greater activation in this region when participants processed symbols as numbers compared

with control tasks on the same symbols. Their study demonstrates two things: first, specificity to symbolic numbers in this region can emerge independently of sensory modality and visual experience and second, that signal drop-out does not systematically prevent preferential activations for numbers in this part of the brain from being found (Piazza & Eger, 2016).

Whether or not symbolic number representations are impaired in adults with DD remains an unresolved question as all of the above suggestions are post-hoc explanations of null findings. Further studies investigating the quality of symbolic number representations in DD might consider to collect more scanning data of only symbolic numbers to increase the signal-to-noise ratio, increase the difficulty of the task by increasing the magnitude range, find their salvation in high-resolution scanning, look into the visual number area, and possibly the combination of all these measures might resolve the issue.

Limitations of DTI In chapter 7, we applied DTI to investigate if adults with DD have altered white-matter connectivity. However, we did not observe any significant differences in any of the white-matter tracks that we analyzed between adults with DD and well matched participants.

We chose DTI tractography, as it has been implemented in all of the diffusion imaging studies regarding numerical cognition, arithmetic and mathematical skills, and dyscalculia in children. However, there is a major limitation to this model that might explain the found null results. The model assumes that, in each voxel, there is a unique orientation of the fibers, the direction of which is represented by the tensor's main eigenvector. This assumption is not valid in case of crossing fibers (Wiegell et al., 2000; Alexander et al., 2001; Barrick & Clark, 2004; Descoteaux et al., 2009). The term "crossing fibers" generally refers to regions in which the fiber's orientation is not unique. Given the relatively large voxel size of diffusion weighted images, the proportion of white matter voxels in the brain that contain multiple fiber orientation has been reported to reach up to 90% (Jeurissen et al., 2013). Therefore, the recon-

structed white-matter tracts via the application of DTI provides an oversimplification of the underlying anatomy.

The last decade, more complex diffusion imaging models are being developed to overcome this issue of DTI, the so called non-tensor models. One such a model is Spherical Deconvolution Tractography (SDT), it can characterize multiple fiber directions per voxel (Dell'Acqua et al., 2013; Tournier et al., 2004). SDT measures the hindrance modulated orientational anisotropy (HMOA), which refers to the absolute amplitude of each lobe of the fiber orientation distribution. It provides information about the diffusion properties along each fiber orientation, in regions with multiple fiber crossings. Therefore, the HMOA index might have an increased sensitivity to detecting microstructural changes in specific white matter tracts, even in regions of crossing fibers.
We have started to delineate one white-matter tract in our DWI data of chapter 6 with this novel method: the three branches of the SLF. We chose to delineate this tract with SDT, as its three segments cannot be accurately delineated from each other by applying the DTI model (Thiebaut de Schotten et al., 2011) and we wanted to investigate if SDT will increase our sensitivity to detect white-matter connectivity differences between adults with and without DD. Results from the application of SDT to the Medial branch of SLF (SLF_1), Middle branch of SLF (SLF_2), and Lateral branch of SLF (SLF_3) failed to find any significant differences between the DD group and the control group, even at uncorrected levels (-0.78 $<$ t-stats $<$ 0.80, 0.68 $<$ p_{FDR} $<$ 0.90). Thus, even with a more sensitive technique, at least for the SLF, we again did not observe altered white-matter connectivity in DD. Further investigation should find out if the application of SDT for the other white-matter tracts (IFOF, ILF, AF, and CC) would have made a difference concerning the observed null results for the white matter tracts in chapter 6.

Important to note for future research, is both DTI and SDT cannot provide information about the actual myelination and axon growth or degeneration in a studied group. It can at best yield *some* insight when they show that *something* in the white-

matter tracts are different. Given the nature of the metrics of DTI and SDT, one is simply unable to say whether this *something* relates to axonal morphometrics, myelin morphometrics, or a combination of the two. Thus while DTI and SDT yield sensitivity, it comes at a price of lack of biological specificity. Therefore it has been suggested that the combination of both models with specific microstructural imaging methods (e.g., myelinated water imaging, (Deoni et al., 2012)), called tractometry, is needed to fully understand the underlying white-matter deficits of neural disorders (D. Jones & Nilsson, 2015).

Domain-specific and domain-general deficits in dyscalculia Many studies have observed domain-specific behavioral and neural deficits in DD, namely impaired number processing and arithmetic skills. However, some other studies have reported impairments in DD on a more domain-general level, such as working memory, inhibition, or attention (Rotzer et al., 2009; Szucs, 2013; Bull et al., 1999; Shalev et al., 1995; Ashkenazi & Henik, 2010).

In chapter 6 and 7 we found deficits in DD pretty much the entire human cortex with a wide variety of neuroimaging techniques. Even though these deficits in regions not directly involved in number processing might reflect domain-general deficits, we must be cautious in this interpretation as we did not include working memory, inhibition, executive functioning, or attention tests in our studies. Therefore, we cannot correlate these neural deficits to these domain-general skills to answer the question which neural deficits are related to the domain-specific and which to the domain-general impairments in DD.

9.1.3 Of arithmetic skills and number representations.

Chapter 8 consists of a short report where we investigated how the overlap in neural representations between dots and digits are correlated with arithmetic skills. Over the course of the chapters 4, 5, and 6 we noticed that the generalization accuracies between digits and dots were varying along the level of arithmetic skills and math-

ematical expertise.

In chapter 8 we explicitly tested this post-hoc hypothesis with the three different type of groups that we scanned: individuals with high arithmetic skills (mostly graduate students or engineers), average arithmetic skills (mostly undergrad students in humanities or languages), and low arithmetic skills (undergrad students with DD). Our results demonstrated that with lower arithmetic skills, one has more overlapping neural representations between symbolic and non-symbolic number processing.

This finding fits with the estrangement account of how symbols acquire their meaning through development (Lyons et al., 2012): in early childhood symbolic representations acquire their meaning through mapping onto non-symbolic representations of number, however, over the course of development and with increasing arithmetic skills these symbols become "estranged" from the non-symbolic representation. This account makes a specific prediction about which relationship one could expect between strength of the mapping between non-symbolic and symbolic representations at the neural level and arithmetic skills. The better the arithmetic skills, the higher the estrangement and thus the weaker the relationship between symbolic and non-symbolic representations.

A major consideration with this chapter, is that this is an effect observed across multiple neuroimaging studies in this dissertation and thus not an explicit experiment performed to answer these questions. However, it certainly gives some insights in how symbols might acquire their meaning and how the association between symbolic and non-symbolic numbers is intertwined with arithmetic skills and experience. Future research should certainly look into this question and can address this by again applying generalization MVPA in more formal experiment with different groups varying in arithmetic skills or different groups varying in age (e.g., children pre-formal schooling age, children in elementary school, adolescents in high school, and adults in college).

9.2 Suggestions for future research

We already applied some of the state-of-the-art advanced neuroimaging techniques in this dissertation to answer some of the pending questions in numerical cognition. In this section, we will make some suggestions for further research applying other advanced neuroimaging analyses to further advance the numerical cognition field.

9.2.1 fMRI Paradigm

In all of the functional neuroimaging studies in this doctoral dissertation, we used a similar fMRI paradigm: a direct number comparison task. In this paradigm, the participant had to immediately compare the presented number to a reference number. The disadvantage of this paradigm is that we cannot separate the number representations from the comparison process. This might be crucial as Nieder et al. (2006) demonstrated in a neurophysiological study that parietal neuronal responses could generalize across presentation modes (but not format) as a result of working memory processes during a number comparison task. Therefore, Eger (2016) suggested that fMRI activity can reflect format-specific and format-invariant number characteristics and that these invariant components could be hard to detect, especially in situations of a direct comparison. It would be interesting in further research to investigate the influence on number representations of a direct versus a delayed number comparison paradigm.

Another methodological consideration regarding our fMRI paradigm, is that we only included one-digit numbers. We chose this for two reasons. *First*, chapter 4 was mainly based on the study of Eger et al. (2009). Eger and colleagues (2009) had also used in their second experiment the magnitudes 2, 4, 6, and 8 in both symbolic and non-symbolic format. We opted for the same paradigm to easily compare our result to theirs and to see if high-resolution scanning is necessary to decode the neural representations of dots and digits.

Second, it is not yet known how the neural representations of two-digit numbers are related to 1-digit numbers. For example, digit 15, can consist of a combination of the neural representations of digit 1 and digit 5, or there could be a completely separate neural representation for digit 15. To investigate this, one could do a event-related fMRI experiment with a passive viewing task and several individual one-digit numbers and their combination to two-digit numbers. The same MVPA method as Macevoy & Epstein (2009) and Baeck et al. (2013) can be then be applied. MacEvoy and Epstein (2009) concluded that when presenting two objects together, the object pair elicits a response pattern that is close to the average of the response patterns associated with the two objects when presented in isolation. If this is universally true for numerical stimuli, then one could expect a very similar response pattern between the one-digit numbers (e.g., "1" and "5") and their combination in to a two-digit number (e.g., "15')'.

Important to note, is that the signal-to-noise ratio for symbolic representations are extremely low as discussed above and therefore, it might be could to consider to collect the data for these experiments on a high-resolution MRI scanner (e.g., 7T-scanner) to increase the signal-to-noise ratio.

9.2.2 Combining MVPA and adaptation

The chapter 4 and 5 of this dissertation provided clear evidence against the format-independent hypothesis. Other MVPA studies confirming our results in the parietal cortex have been reported (Damarla & Just, 2012; Lyons et al., 2015).

On the other hand, there are several adaptation fMRI studies that demonstrate evidence in favor of format-independent hypothesis in the IPS (Ansari, 2007; Cohen Kadosh et al., 2007; Dehaene et al., 2003; Naccache & Dehaene, 2001; Piazza et al., 2010, 2011, 2007; Zago et al., 2001).

The discrepancies between the MVPA fMRI studies and adaptation fMRI studies might

be due to some drawbacks of MVPA fMRI. Davis & Poldrack (2013) reported some pitfalls of MVPA: MVPA is less efficient in estimations about changes across time, less good to make strong conclusions about the anatomical localization of an effect in larger ROIs, and it would fail to measure representations in contexts where an entire stimulus space is represented in a single voxel.

This last drawback is one of the greatest advantages of adaptation fMRI which is the only method that can measure representational relationship across neurons in a single voxel (Davis & Poldrack, 2013). Although adaptation fMRI has this great advantage over MVPA, it is not pitfall-free either. Namely, adaptation does not always correspond in an one-to-one manner to the underlying neural code and might be influenced by top-down processing and subjects' goals. For example, neuronal adaptation has been shown to be less than expected for two stimuli that a neuron was equally sensitive to relative to exact stimulus repetitions, suggesting that, in some cases, comparing adaptation effects between two different stimuli and exact repetitions may overestimate the representational specificity (Davis & Poldrack, 2013).

To combine the strengths of both fMRI methods, a continuous carry-over design can be applied (Aguirre, 2007). A continuous carry-over design is an event-related fMRI experiment that allows us to analyze the data both with adaptation fMRI and MVPA fMRI. Therefore, the strengths of both techniques are combined, where adaptation can measure representational relationships coded across neurons encompassed within a single voxel and MVPA allows for measuring combination effects across voxels and has greater sensitivity than other fMRI techniques (Davis & Poldrack, 2013). This design has the potential to further unravel how numbers are represented in the brain and how previous contradicting results can be conjoined.

9.2.3 High resolution scanning

Another solution to overcome the MVPA drawback that emerges when an entire stimulus space is represented in one voxel, is to increase the spatial resolution by moving

to higher resolution scanning.

To date, two neuroimaging studies have investigated the nature of number representations with a 7T-scanner. However, the format-independent number representations evidence provided by adaptation studies on 3T-scanners were not found. A first study by He et al. (2014) demonstrated that with increasing numbers, the IPS activity between dots and digits became less similar. Another study by Harvey et al. (2013) showed a clear topographic representation of numerical magnitude in human parietal cortex, but only for dot patterns and not for digits.

This latter finding is not that surprising in the light of chapter 5 of this dissertation. Based on the object cognition account, one would expect that all the 1-digit numbers would be mapped onto the one dot area in the topographic representation of the numbers.

To test this hypothesis, we have started up a 7T-study where we used the paradigm by Harvey et al. (2013) to replicate the topographic maps of non-symbolic representations in the parietal cortex in each participant. Furthermore, we also collected the 7T data with the same paradigm as in chapter 4 (Figure 9.1). The participant specific topographic map of non-symbolic representations then serves as a ROI to apply the same generalization and confusion analyses as in chapter 5. The first two (out of ten) participants have been already analyzed with this design, and we observed a generalization accuracy of 51% (again at chance level) and a confusion of digits with one dot (instead of dot condition sharing the same magnitude) of 72%. Although, the other participants have to be analyzed and many other analyses need to be performed before we can conclude anything, these first pilot results align well with the evidence we provided in chapter 4 and 5.

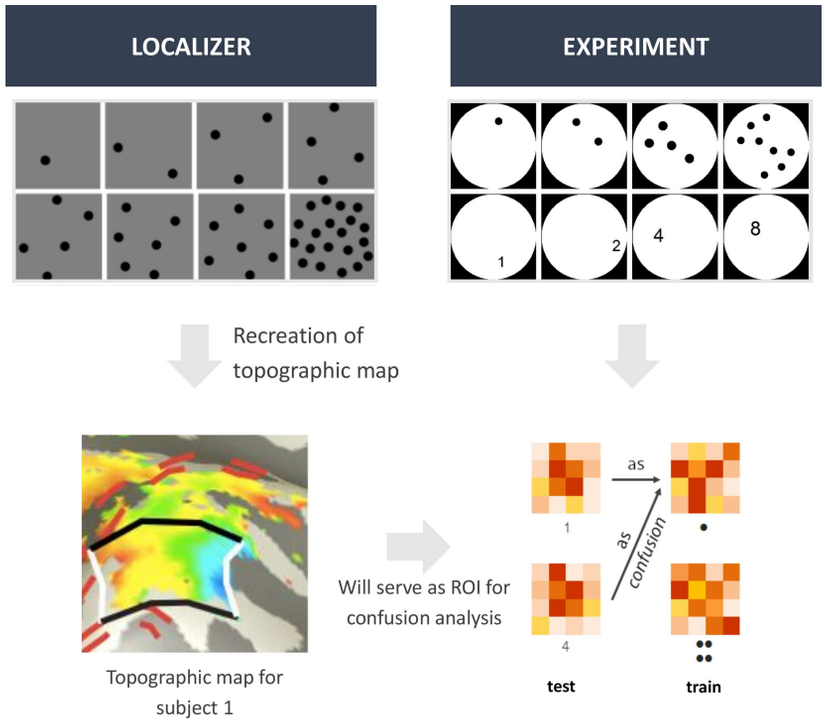

Figure 9.1: Overview of the 7T Experiment. The paradigm and analyses applied by Harvey et al. (2013) are used to recreate the topographic map in each participant. We also performed exactly the same paradigm as in chapter 5 with the topographic map as ROI.

9.3 Conclusion

It is clear that we have made several important advances in this dissertation for the numerical cognition field by the application of advanced neuroimaging techniques. However, it is important to comprehend that we are still left with many outstanding questions and considerations regarding number processing in the human cortex that are in need of answers. At the end of this final chapter, we have given several experimental ideas to further advance the numerical cognition field with standard and advanced neuroimaging techniques. To conclude with Albert Einsteins words: *the important thing is to never stop questioning*.

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Curriculum Vitae

Jessica Bulthé was born on December 7th, 1988 in Rocourt (Belgium). She spent most of her childhood in Ternat, Belgium. She followed her secondary education at Sint-Jozefscollege (Ternat) with majors in Economics and Mathematics, where she graduated cum laude in 2006. She attended the KU Leuven, from which she obtained a Psychology degree, magna cum laude, at Faculty of Psychology and Educational Sciences in 2011. In 2011, she started a PhD at Brain & Cognition Laboratory supervised by Prof. Dr. Hans Op de Beeck and co-supervised by Prof. Dr. Bert De Smedt. In 2012, she received a grant from the Research Foundation Flanders (FWO) to fund her research. She married Jan Bouckaert in 2013 and gave birth to a son, Wannes Bouckaert, in 2016.

List of publications

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1. **Bulthé, J.**, De Smedt, B., Op de Beeck, H. (2015). Visual number beats abstract numerosity: Format-dependent representations of Arabic digits and dot patterns in the human parietal cortex. Journal of Cognitive Neuroscience, 27 (7), 1376-1387.

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2. **Bulthé, J.**, De Smedt, B., Op de Beeck, H. Arithmetic skills correlate negatively with overlap of symbolic and non-symbolic number representations.

3. **Bulthé*, J.**, Vanderauwera*, J., Gillebert, C., Mantini, D., Op de Beeck, H., De Smedt, B. Altered connectivity in adults with dyscalculia.

4. Martens, F., **Bulthé, J.**, van Vliet, C., Op de Beeck, H. Domain-general and domain-specific neural changes underlying visual expertise.

5. Peters, L., **Bulthé, J.**, Op de Beeck, H., De Smedt, B. Arithmetic in dyscalculia and dyslexia: Different behavioral, yet similar brain activity.

Conference abstracts

1. **Bulthé, J.**, Prinsen, J., Vanderauwera, J., Duyck, S., Daniels, N., Gillebert, C., Mantini, D., De Smedt, B., Op de Beeck, H. (2017). Multi-method brain imaging reveals impaired representations as well as altered connectivity in adults with dyscalculia. OHBM 2017 (Organization for Human Brain Mapping). Vancouver, Canada, 25-29 June 2017. *Poster Presentation; Abstract Merit Award*

2. **Bulthé, J.**, Op de Beeck, H., De Smedt, B. (2017). Arithmetic skills correlate negatively with overlap of symbolic and non-symbolic number representations. Groupe de Contact "Numbers and the Brain". Tournai, Belgium, 4-5 May 2017. *Oral Presentation*

3. **Bulthé, J.**, Prinsen, J., Vanderauwera, J., Duyck, S., Daniels, N., Gillebert, C., Mantini, D., De Smedt, B., Op de Beeck, H. (2017). Multi-method brain imaging reveals impaired representations as well as altered connectivity in adults with dyscalculia. Scientific Meeting of The Royal Society, London: The origins of numerical abilities. London, UK, 20-21 February 2017. *Poster Presentation*

4. **Bulthé, J.**, Prinsen, J., Vanderauwera, J., Duyck, S., Daniels, N., Gillebert, C., Mantini, D., De Smedt, B., Op de Beeck, H. (2017). Multi-method brain imaging reveals impaired representations as well as altered connectivity in adults with dyscalculia. Scientific Meeting of The Royal Society, London: The origins of numerical abilities. London, UK, 20-21 February 2017. *Poster Presentation*

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6. **Bulthé, J.**, Prinsen, J., Vanderauwera, J., Duyck, S., Daniels, N., Gillebert, C., Mantini, D., De Smedt, B., Op de Beeck, H. (2016). Multi-method brain imaging reveals impaired representations as well as altered connectivity in adults with dyscalculia. NeurCog. Leuven, Belgium, 28-29 November 2016. *Poster Presentation*

7. Martens, F., **Bulthé, J.**, van Vliet, C., Op de Beeck, H. (2016). Domain-general and domain-specific neural effects of visual expertise. NeurCog. Leuven, Belgium, 28-29 November 2016. *Poster Presentation*

8. Peters, L., **Bulthé, J.**, Op de Beeck, H., De Smedt, B. (2016). Arithmetic in dyscalculia and dyslexia: Different behavioural, yet similar brain activity profiles. NeurCog. Leuven, Belgium, 28-29 November 2016. *Poster Presentation*

9. Peters, L., **Bulthé, J.**, Op de Beeck, H., De Smedt, B. (2016). Arithmetic in children with dyslexia, dyscalculia and comorbid dyslexia/dyscalculia: Different behavioral, yet similar brain activity profiles. IMBES. Toronto, Canada, 15-17 September 2016. *Poster Presentation*

10. Peters, L., **Bulthé, J.**, Op de Beeck, H., De Smedt, B. (2016). Arithmetic in children with dyslexia, dyscalculia and comorbid dyslexia/dyscalculia: Different behavioral, yet similar brain activity profiles. Flux: The International Society for Integrative Developmental Cognitive Neuroscience. St. Louis (MO), USA, 8-10 September 2016. *Poster Presentation*

11. Peters, L., **Bulthé, J.**, Op de Beeck, H., De Smedt, B. (2016). Arithmetic in children with dyslexia, dyscalculia and comorbid dyslexia/dyscalculia: Different behavioral, yet similar brain activity profiles. SIG15 Special Educational Needs. Leuven, Belgium, 29-30 August 2016. *Poster Presentation*

12. Peters, L., **Bulthé, J.**, Op de Beeck, H., De Smedt, B. (2016). Arithmetic in children with dyslexia, dyscalculia and comorbid dyslexia/dyscalculia: Different behavioral, yet similar brain activity profiles. SIG22 Neuroscience and Education meeting. Amsterdam, The Netherlands, 23-25 June 2016. *Poster Presentation*

13. **Bulthé, J.**, Prinsen, J., Vanderauwera, J., Duyck, S., Daniels, N., Gillebert, C., Mantini, D., Op de Beeck, H., De Smedt, B. (2016). Impaired neural representations of non-symbolic numbers in adults with dyscalculia. Groupe de Contact "Numbers and the Brain". Kortrijk, Belgium, 21-22 April 2016. *Oral Presentation*

14. Peters, L., **Bulthé, J.**, Op de Beeck, H., De Smedt, B. (2016). The neural differences and similarities between children with and without learning disorders

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17. Prinsen, J., **Bulthé, J.**, Op de Beeck, H., De Smedt, B. (2015). Dyscalculia in Adults: Neural Representations in the Human Cortex. Belgian Association for Psychological Sciences. Brussels, Belgium, 28 May 2015. *Poster Presentation*

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19. **Bulthé, J.**, De Smedt, B., Op de Beeck, H. (2014). Visual number beats abstract numerosity: format-dependent neural representations of numbers in the parietal cortex. LIND seminar. Mechelen, Belgium, 5 December 2014. *Poster Presentation; Best Poster Presentation Award*

20. **Bulthé, J.**, De Smedt, B., Op de Beeck, H. (2014). Visual number beats abstract numerosity: Format-dependent representations of Arabic digits and dot patterns in the human parietal cortex. SFN. Washington D.C., USA, 15-19 November 2014. *Poster Presentation*

21. **Bulthé, J.**, Op de Beeck, H., De Smedt, B. (2014). Format-dependent neural representations of numbers as revealed by multi-voxel pattern analysis. SIG 22. Gottingen, Germany, 12 - 14 June 2014. *Poster Presentation*

22. **Bulthé, J.**, Op de Beeck, H., De Smedt, B. (2014). Visual number beats abstract numerosity: format-dependent representation of Arabic digits and dot patterns in the human parietal cortex. Groupe de Contact "Numbers and the Brain". Louvain-La-Neuve, Belgium, 24-25 April 2014. *Oral Presentation*

23. **Bulthé, J.**, Op de Beeck, H., De Smedt, B. (2014). Format-dependent neural representations of numbers as revealed by multi-voxel pattern analysis. Expert meeting of the researchers of mathematical thinking and learning of the Netherlands, Belgium and Luxembourg. University of Leiden, the Netherlands, 4 April 2014. *Poster Presentation*

24. **Bulthé, J.**, De Smedt, B., Op de Beeck, H. (2014). Do it yourself: searchlight analysis. ABC advanced neuroimaging curriculum: Pattern analysis and classification. Amsterdam, the Netherlands, 29-31 January 2014. *Invited Oral Presentation*

25. **Bulthé, J.**, De Smedt, B., Op de Beeck, H. (2013). Neural Representations of Numbers in the Human Cortex. Workshop on Concepts, Action and Objects. Rovereto, Italy, 24-26 May 2013. *Poster Presentation*

26. **Bulthé, J.**, Op de Beeck, H., De Smedt, B. (2013). Neural representations of numbers in the human cortex. Groupe de Contact "Numbers and the Brain". Mozet, Belgium, March 2013. *Oral Presentation*

27. **Bulthé, J.**, Op de Beeck, H., De Smedt, B. (2013). Neural representations of numbers in the cortex: a multilevel voxel pattern analysis approach to the numerical distance effect. Expert meeting of the researchers of mathematical thinking and learning of the Netherlands, Belgium and Luxembourg. University of Luxembourg, 1 March 2013. *Poster Presentation*

28. Peters, L., **Bulthé, J.**, Op de Beeck, H., De Smedt, B. (2013). Neural representations in visual cortex for numerical magnitudes presented in different formats. Society for Neuroscience. San Diego, USA, 9-13 November 2013. *Poster Presentation*

29. **Bulthé, J.**, Op de Beeck, H., De Smedt, B. (2012). Neural representations of numbers in the cortex: a multilevel voxel pattern analysis approach to the numerical distance effect. Belgian Brain Congress. Liege, Belgium, 27 October 2012. *Poster Presentation*

30. **Bulthé, J.**, Op de Beeck, H., De Smedt, B. (2012). Neural representations of numbers in the cortex: a multilevel voxel pattern analysis approach to the numerical distance effect. Beijing International Conference on the Neuroscience of Mathematical Cognition and Learning. Beijing, China, June 2012. *Poster Presentation*